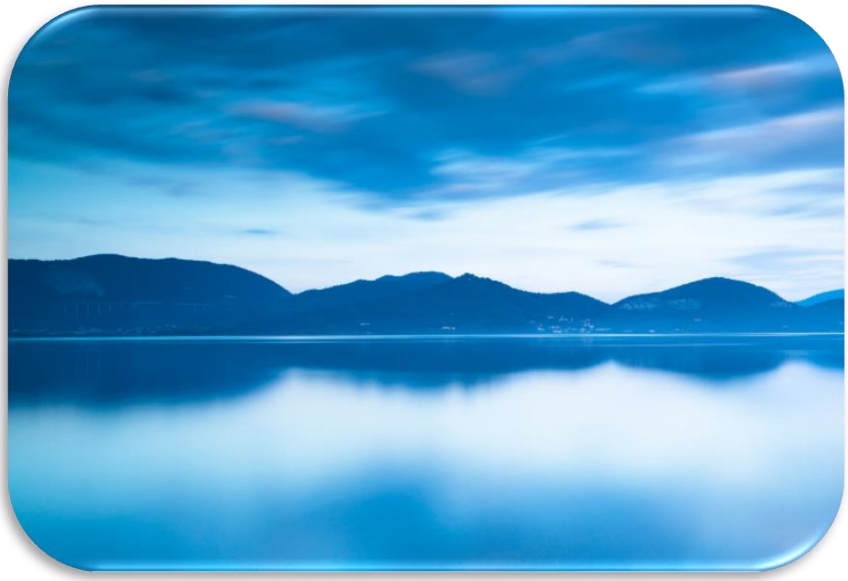
Harms and benefits of e-cigarettes and heat-not-burn tobacco products: A literature map



Authors:
Anne McCarthy
Caitriona Lee
Doireann O'Brien
Jean Long
Date June 2020

Disclaimer

Any views expressed in this report are those of the authors and not necessarily those of the Minister for Health, the Department of Health or Health Research Board

Published by:

Health Research Board, Dublin

t 353 1 234 5000
f 353 1 661 2335
e hrb@hrb.ie
w www.hrb.ie

Table of Contents

List of tables

List of figures

Abbreviations

Abbreviation	Explanation
AAPCC	American Association of Poison Control Centers
Academies of Sciences	United States National Academies of Sciences, Engineering, and Medicine
ADD	attention deficit disorder
AOR	adjusted odds ratio
ARR	adjusted risk ratio or adjusted relative risk
β2*-nAChR	Beta2*-nicotinic acetylcholine receptors
bpm	beats per minute
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
CDC	Centers for Disease Control and Prevention
CO	carbon monoxide
CPAP	continuous positive airway pressure
CT	computed tomography
e-cigarette(s)	electronic cigarette(s)
eCO	exhaled carbon monoxide
EHCSS	electrically heated cigarette smoking system
ENDS	electronic nicotine delivery system
EU	European Union
EVALI (or VALI)	e-cigarette and vaping associated lung injury
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in the first second
FEV1/FVC	forced expiratory ratio
FVC	forced vital capacity
GM	geometric mean
HbA1c	glycated haemoglobin level
HDL	high-density lipoprotein
HRB	Health Research Board
HSE	Health Service Executive
LDL	low-density lipoprotein
LED	light-emitting diode
MeSH	medical subject headings
MMWR	Morbidity and Mortality Weekly Report (Early Release)
NADPH	nicotinamide adenine dinucleotide phosphate oxidase
NIH	National Institutes of Health
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

Abbreviation	Explanation
NNN	N'-Nitrosonornicotine
NRT	nicotine replacement therapy
OR	odds ratio
ppm	parts per million
PEF	peak expiratory flow
PICO	Population, intervention or exposure, comparator and outcome
RCT	randomised controlled trials
RR	risk ratio (sometimes known as relative risk)
r^2	regression [measure]
RCT	randomised controlled trial
RPP	rate-pressure-product
SE	standard error
SpO_2	oxygen saturation, measured by pulse oximetry
THS	tobacco heating system
TNF-alpha	tumour necrosis factor-alpha
TSNAs	tobacco specific N-nitrosamines
UK	United Kingdom
USA	United States of America
WBC	white blood cells
WHO	World Health Organization

Summary

Purpose

In 2013, the Tobacco Policy Review Group published *Tobacco Free Ireland*, a report which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025. The report identified tobacco-related harm reduction as a key issue for consideration. Since e-cigarettes' launch in the European Union (EU) in 2006 and in the United States of America (USA) in 2007, research on their potential benefits in terms of tobacco-related harm reduction, and on their public health harms, has grown. This mapping exercise describes the nature and extent of the literature on the public health harms and benefits of e-cigarettes and heat-not-burn tobacco products to the human population. An e-cigarette is an umbrella term for an electronic device that delivers nicotine and other products including flavourings while a heat-not-burn tobacco product is an umbrella term for devices that heat but do not burn tobacco. They have similar but not identical yields of tar, nicotine, and other products, such as carbon monoxide.

Research question

This research addresses two questions posed by the Irish Department of Health:

1. What are the public health benefits and harms of e-cigarettes?
2. What are the public health benefits and harms of heat-not-burn tobacco products?'

Methods

Mapping exercises provide an overview of the nature and extent of the available evidence, with limited description of the data. The mapping period covers peer review literature published between January 2005 and November 2019 on e-cigarettes, and between January 1988 and November 2019 for heat-not-burn tobacco products. Comprehensive searches were completed and updated three times during the mapping period. The mapping exercise was completed between April 2019 and January 2020. The literature was retrieved from seven databases and one search engine – Ovid MEDLINE, Cochrane Library, Ovid PsycINFO, Elsevier Embase, PROSPERO, LILACS, CORE.ac.uk and Google Scholar. There were three rounds of screening, using predefined inclusion and exclusion criteria, to identify the papers included in this review. The study summaries are presented, or arranged, by headings (epidemiological study design with the addition of surveillance reports) and subheadings (dependence and abuse liability; cardiovascular diseases; cancers; respiratory diseases; oral diseases; developmental and reproductive effects; and injuries and poisonings) in order to describe, design and develop effective research questions and programmes. The subheadings were adapted from the United States National Academies of Sciences, Engineering, and Medicine.

The authors of this mapping exercise added two further headings – exposure to e-cigarette toxins, and other outcomes – in order to categorise literature that did not align under the existing headings. Harms and benefits could be the result of either use of, or exposure to, e-cigarettes or e-liquid or heat-not-burn tobacco products.

The outcomes measured were clinically diagnosed diseases or injuries, biological risk markers for disease, measures of organ function, presence of toxins and toxicants, and self-reported signs and symptoms.

Findings

This mapping exercise describes findings from published peer reviewed journal articles and organises the information in a way that enables discussion and decision-making by researchers, policy makers, and practitioners. This mapping exercise describes findings from published peer-reviewed journal articles which examine the relationship between two nicotine-related products and their impact on human health. We identified 388 papers eligible for inclusion in the map, 361 reporting the harms and benefits of e-cigarettes, and 28 reporting the harms and benefits of heat-not-burn tobacco

products, with one paper reporting both exposures. An e-cigarette is an umbrella term for a device that delivers nicotine and other products including flavourings while a heat-not-burn tobacco product is an umbrella term for devices that heat but do not burn tobacco. They have similar but not identical yields of tar, nicotine, and other products, such as carbon monoxide.

E-cigarette summary map

The 361 included studies on possible harms and benefits of e-cigarettes were mapped by study design and by the adapted Academies of Sciences' umbrella terms. All types of epidemiological study designs were used to investigate the recent e-cigarette phenomenon. The highest number of studies were case reports, followed by interventional trials and then cross-sectional surveys. Papers reporting surveillance data are also presented as they characterise clinical presentation of the harms and benefits of e-cigarettes at a community-level. The e-cigarette-related health harms, harm reduction, and benefits known to date are presented in this mapping exercise. However, there may be unknown harms.

Most of our observed clinical harms were due to acute harmful events associated with the use of e-cigarettes and were reported in descriptive case reports, case series, surveillance system papers, and cross-sectional survey papers (Table A). They included poisonings (mainly nicotine and some e-liquid constituents), injuries (mainly burns and some fractures), and respiratory diseases (mainly injuries to the lungs and exacerbation of asthma). There were fatalities among the poisonings and respiratory disease cases, and long-term disability among some burn cases. Both the poisoning cases and the respiratory disease cases highlighted a possible association between e-cigarettes and the use of other drugs such as alcohol, synthetic cannabinoids, and opiates. There was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds. Four cross-sectional surveys on cancers identified the presence of carcinogens for lung, oral, and oesophageal cancer, and one identified biomarkers for bladder cancers. Some respiratory, cardiovascular, and oral diseases were noted to be less harmful in e-cigarette users than in conventional cigarette smokers, but were as harmful as in dual users (i.e. users of both conventional tobacco cigarettes and e-cigarettes) (Table B). However, these respiratory, cardiovascular, and oral disease findings were not consistent across all studies.

The evidence map featured few reported benefits (Table C). The most common benefits, which were reported by a small number of heavy smokers of conventional tobacco cigarettes, were smoking cessation and smoking reduction. Alongside this map, two systematic reviews on e-cigarettes were completed by the HRB. In the first review, we found that e-cigarettes were not more effective than approved nicotine replacement therapies (NRTs), which questions the need for e-cigarettes as a smoking cessation intervention. In the second review, we found that e-cigarettes were associated with initiation of conventional cigarette smoking among adolescents, which identifies a potentially serious harm.

In addition, we note that many studies showed that dual use of both e-cigarettes and conventional tobacco cigarettes was not less harmful than smoking conventional tobacco cigarettes alone, thereby raising questions about the smoking reduction benefit of e-cigarettes.

Generally, our thematic findings align with the high-level findings of six reviews and have some contrasting findings with a seventh systematic review. Given the time gap between the existing systematic reviews and our mapping exercise, we identified additional recent papers covering oral diseases, and developmental and reproductive effects associated with e-cigarettes.

Table A Possible e-cigarette-related negative outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Possible harms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Probable harms			1	18		6	9
Cardiovascular diseases	Probable harms	2	1	.	3	.	1	15
Cancers	Probable harms		1		2	1		1
Respiratory diseases	Probable harms	20	8	4	16	1 Tetrahydrocannabinol	3	15
Oral diseases	Probable harms	4			11		1	1
Developmental and reproductive effects	Probable harms			1			1	
Injuries	Probable harms	28	19	4		.		
Poisonings	Probable harms	21	5	23				
Exposure to e-cigarette toxins	Probable harms	4		1	6			5

Table B Possible e-cigarette-related harms, but less harmful than those related to conventional tobacco cigarettes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Possible harm reduction	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Possible harm reduction				1		1	5
Cardiovascular diseases	Possible harm reduction				1		1	3
Cancers	Possible harm reduction				3			
Respiratory diseases	Possible harm reduction				3		3	5
Oral diseases	Possible harm reduction				2		2	
Developmental and reproductive effects				No harm reduction identified				
Injuries				No harm reduction identified				
Poisonings				No harm reduction identified				
Exposure to e-cigarette toxins	Possible harm reduction				4			8

Table C Possible e-cigarette-related beneficial outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Possible benefits	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Possible benefits		2		2		6	7
			Not more effective than NRTs					
Cardiovascular diseases	Possible benefits		No benefits identified					
Cancers	Possible benefits		No benefits identified					
Respiratory diseases	Possible benefits	2						2
Oral diseases	Possible benefits							1
Developmental and reproductive effects			No benefits identified					
Injuries			No benefits identified					
Poisonings			No benefits identified					
Exposure to e-cigarette toxins	Possible benefits							1

The peer-reviewed published studies were drawn from all over the Globe, with the highest number from the USA, followed by Italy. The study participants were mainly adults. However, young children were common in studies examining injuries and poisonings. Never-smokers were also observed to use e-cigarettes.

The study designs were a mix of randomised controlled trials, randomised and non-randomised crossover trials including Latin square trials, and non-randomised before and after studies. The follow-up periods in the mapped studies ranged from minutes to 24 months and did not have a sufficient timeframe to detect chronic disease outcomes such as cardiovascular diseases, cancers, or chronic respiratory diseases. For example, a total of 8 (9%) of the 86 interventional trials reported on an exposure outcome effect measured between 12 weeks and 24 months, while the remaining 78 trials reported on outcomes measured within 8 weeks or less. It is important to note that e-cigarettes and their e-liquids were not a standard intervention in the included studies; rather, they are an umbrella term for a device that delivers nicotine and other products including flavourings. By 2017, 611 brands of e-cigarette products had been developed, and to generalise findings from the randomised trial of one specific e-cigarette as an assessment of the expected impact of all e-cigarette types discounts the differences in the chemical composition of various e-cigarette brands and types. The content of the e-liquids was another confounding factor due to the variation in nicotine dosages and other contents. To date, of the 86 trials examining health benefits and harms in people included in the map, only 62 trials identified the device used and only 39 e-cigarette devices were tested out of

more than 611 brands ever available on the market, which gives a sense of the small number of e-cigarette devices that have been tested in trials involving people, and the small number of corresponding research papers published in peer-reviewed literature. A total of 9% of the interventional trials were completed by the e-cigarette industry. Care must be taken in the area of e-cigarettes when generalising findings from the studied populations to other populations with different characteristics, and when generalising findings from populations where different kinds of interventions (e-cigarettes) were used. Most of the observational and interventional studies identify associations between e-cigarettes and the outcomes of interest, but these associations do not prove causality.

Heat-not-burn tobacco products summary map

Heat-not-burn tobacco products were not authorised for sale in Ireland by February 2020. The 28 included published, peer-reviewed studies on possible harms and benefits of heat-not-burn tobacco products have been mapped by study design and by the adapted umbrella terms identified by Academies of Sciences'. There were two case reports and one cross-sectional survey covering these products. There were 25 interventional trials, 23 of which were completed by authors working in the tobacco industry and 2 of which were completed by authors in universities, indicating a dearth of independent research on heat-not-burn tobacco products. Among the 25 published interventional trial papers, just under half (12) reported biomarkers of exposure to harmful or potentially harmful smoke constituents (Table D). Eight interventional trial papers reported outcomes of cardiovascular health, and this represented the second most reported area of interest. One crossover interventional trial paper reported on measures of respiratory function, and four interventional trial papers reported on measures of dependence and abuse liability.

The possible harm and benefit outcomes measured under the 'dependence and abuse liability' heading included cigarette craving/urge to smoke, withdrawal symptoms, nicotine and its metabolites, and various measures of carbon monoxide. The outcomes measured under the 'cardiovascular diseases' heading included a wide range of biomarkers that may indicate organ and tissue damage. The reported respiratory outcomes included measures of airway resistance, lung function, and lung volume. The outcomes measured under the 'exposure to heat-not-burn toxins' heading were an extensive array of harmful or potentially harmful constituents of conventional tobacco cigarette smoke.

The overall conclusions of the primary study authors were that the impacts of heat-not-burn tobacco constituents measured for cardiovascular and respiratory health and well-being may be less harmful than those of conventional tobacco cigarettes, but more harmful than those observed in study participants who abstained from smoking. In a similar fashion, lower levels of the measured harmful and potentially harmful constituents in cigarette smoke were present in heat-not-burn tobacco product users than in smokers of conventional combustible tobacco cigarettes, but the lowest levels of these harmful and potentially harmful constituents were observed in study participants who abstained from smoking during the study period. However, the long-term consequences of these outcomes cannot be addressed by the study designs examined in this mapping exercise.

Our findings on heat-not-burn tobacco products agreed with two recent systematic reviews, in that, the measured harmful and potentially harmful constituent levels were lower in heat-not-burn tobacco product users relative to the conventional cigarette user and that most research on heat-not burn tobacco products was industry funded. The review by the World Health Organization concluded the there is insufficient evidence to conclude that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. In fact, the Organization concluded that the there is insufficient evidence to deem that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. The Organization goes on to say that there are reservations, as heat-not-burn tobacco products may expose users to lower levels of some toxicants than conventional tobacco cigarettes, but they may also expose users to higher levels of other toxicants, and it is not clear how this toxicological profile transforms into short- and long-term health effects.

Table D Possible heat-not-burn tobacco product-related negative outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	No studies	No studies	No studies	Perceived stress (N=1)	No studies	No studies	Indicators of nicotine craving (N=3) Nicotine metabolites and concentration curves (N=2)
Cardiovascular diseases	No studies	No studies	No studies	No studies	No studies	No studies	Indicators of cardiovascular health (N=8)
Cancers	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Respiratory diseases	Acute eosinophilic pneumonia (N=2)	No studies	No studies	No studies	No studies	No studies	Indicators of respiratory function (N=1)
Oral diseases	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Developmental and reproductive effects	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Injuries	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Poisonings	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Exposure to heat-not-burn toxins	No studies	No studies	No studies	No studies	No studies	No studies	A range of harmful or potentially harmful smoke constituents (N=12)

In general, study participants were adults. However, there were some exceptions: adolescents were the subject of one cross-sectional study, and a 16-year-old male was the subject of one case report. Approximately half of the studies were conducted in Belgium, Italy, Poland, South Africa, the UK, and the USA, and approximately the same number were conducted in Asia (Japan and South Korea). The two case reports each described one individual's experience of acute eosinophilic pneumonia; the cross-sectional survey reported findings from 60,040 participants, and the sample sizes in the remaining papers (all interventional trials) varied from 18 to 316 participants.

The majority of trials were classified as randomised controlled trials, or crossover trials. The time frames of 24 of the 25 interventional trials were short; outcomes were gathered within a 10-day period or less. For the remaining trial, outcomes were gathered for 24 weeks. Biological measures were frequently gathered minutes or hours after exposure. The data collection time frames were adequate to report on transient effects following short-term heat-not-burn tobacco product use, but not the possible deleterious effects arising from long-term exposure. In general, the impact of heat-not-burn tobacco product use on outcomes beyond the short trial timeframe parameters was not quantified. The mapped interventional trials' follow-up periods were not long enough to detect heat-not-burn chronic disease outcomes such as cardiovascular diseases, cancers, or chronic respiratory

diseases. No peer-reviewed studies on humans were published on cancers, oral diseases, or developmental and reproductive effects up to mid-November 2019. There were no acute poisonings or injuries as a result of heat-not-burn tobacco products. We note that the majority of trials reporting on this area have compared a small number of commercially available heat-not-burn tobacco products with a range of conventional combustible tobacco cigarettes, both releasing varying chemical yields. In a number of trials, comparisons have also been made with persons who have abstained from smoking for the trial duration or for a period during a crossover trial.

It is important to note that heat-not-burn tobacco products were not standardised interventions (i.e. products), but rather that 'heat-not-burn tobacco products' is an umbrella term for devices with similar but not identical yields of tar, nicotine, and other products, such as carbon monoxide. There was variation in the types of devices examined, the chemical yield of the devices, and the trial comparator products used. Data on the chemical yield of the comparator conventional cigarette were not always available, as in several trials, participants were asked to bring and smoke their own preferred brand of conventional tobacco cigarettes.

Long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the nicotine product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of heat-not-burn tobacco products and e-cigarettes, have a positive or negative impact on later life health outcomes.

Research gaps

The reporting framework used in this mapping exercise allows a clear view of the published, peer-reviewed, English-language research which has been undertaken to assess the impacts of e-cigarettes and heat-not-burn tobacco products on human health. The evidence map will serve as a framework for developing questions for scientific appraisal of the nature and direction of the observed relationship within different population groups and different clinical areas. The combination of the hierarchy of evidence and the adapted Academies of Sciences' umbrella terms was a very useful method for categorising the retrieved papers. Presenting the papers in this way highlights that some areas are well described using epidemiological studies, but that there is a dearth of longitudinal cohort studies with well-designed protocols that capture the true effects of e-cigarettes and heat-not-burn tobacco products. Long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of e-cigarettes and heat-not-burn tobacco products, have a positive or negative impact on later life health outcomes. The multitude of possible outcomes require targeted long-term cohort studies to answer research questions under all of the adapted Academies of Sciences' umbrella terms in order to quantify outcome-specific differences between conventional cigarette smokers, e-cigarette users, heat-not-burn tobacco product users, dual users of any combination of these product types, and non-users of any type of cigarette. In the absence of long-term studies, modelling of levels of biological markers for exposure to harmful or potentially harmful constituents in cigarette smoke may allow us to gain a preliminary understanding of some adverse effects of e-cigarettes and heat-not-burn tobacco products. At present, the USA, among other countries, is identifying the research needs, solutions, and funding requirements to progress an understanding of the health effects of e-cigarettes and heat-not-burn tobacco products. It should be noted that there may be unknown harms which are yet to be identified. Some specific research areas that need to be examined thoroughly are the effects of deposits and accumulation of toxins from e-cigarettes and heat-not-burn tobacco products on respiratory, cardiovascular, neurological, and other body tissues; this will also require long-term studies examining the incidence of degenerative diseases and cancers among e-cigarette and heat-not-burn tobacco product users. In addition, preliminary data indicate that a thorough examination of the effects of e-cigarettes and heat-not-burn tobacco products on embryos and newborns is required.

There are four areas which we believe would enhance our understanding of the impacts not only of e-cigarettes and heat-not-burn tobacco products, but also of other tobacco-related products that people can smoke, chew, or sniff. First, the comparison populations regarding smoking-related behaviours must be clearly defined. Second, heterogeneity in the chemical yields and in the

temperature at which the tobacco is heated for both the heat-not-burn tobacco products and the comparison conventional tobacco cigarettes needs to be closely examined and more clearly delineated in order to detect meaningful findings. Third, what, if any, difference do changes in levels of biomarkers of exposure to harmful or potentially harmful vapour or smoke constituents have on the subsequent development of associated deleterious outcomes needs to be understood. Fourth, there is a dearth of longitudinal information on specific populations where evidence on the impact of e-cigarettes could clearly contribute to public health policy formation.

1 Introduction

1.1 Policy background

In 2013, the Department of Health's Tobacco Policy Review Group published the report *Tobacco Free Ireland*, which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025.[2] *Tobacco Free Ireland* was the first policy document to be launched under the Healthy Ireland framework, and it was endorsed by the Government. Achieving the target in the reduction of smoking prevalence would play a major role in realising the vision set out in Healthy Ireland.

The *Tobacco Free Ireland* report identified tobacco-related harm reduction as a key issue for consideration.[2] It specifically highlighted the role of electronic cigarettes (e-cigarettes) as a potential harm reduction strategy. Since the introduction of e-cigarettes in 2006, research has expanded on their potential benefits in terms of tobacco-related harm reduction and on the public health harms of e-cigarettes. This mapping exercise outlines what is known to date about e-cigarette benefits, harm reduction, and harms to humans, which will help to inform the Department of Health's policy position with respect to e-cigarettes.

The Department of Health asked the Health Research Board (HRB) to complete a programme of research and answer five research questions:

1. What are the public health benefits and harms of e-cigarettes?
2. What are the public health benefits and harms of heat-not-burn tobacco products?
3. What is the efficacy of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation)?
4. What is the efficacy of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation)?
5. Does e-cigarette use by adolescents who are cigarette naive at baseline lead to subsequent cigarette smoking?

1.2 Research questions

The questions addressed in this mapping exercise are:

3. What are the public health benefits and harms of e-cigarettes?
4. What are the public health benefits and harms of heat-not-burn tobacco products?

The HRB authors defined public health harms as both clinically diagnosed pathological outcomes (diagnosis of disease or injury) and damage or an injury to biological tissue which can have a short- or long-term outcome leading to disease. We defined public health benefits as when a substance, or activity improves health.

When we use the term conventional tobacco cigarettes in the text, we mean conventional combustible tobacco cigarettes.

2 Background

2.1 E-cigarettes

The aim of the background section is to provide an understanding of e-cigarettes. Due to time limitations, the background section on e-cigarette relies heavily on one high-quality peer-reviewed document by Academies of Sciences, Engineering, and Medicine and an infographic from the National Institute on Drug Abuse.

It is generally accepted that e-cigarettes were introduced to Europe in 2006 and to the USA in 2007. The e-cigarette economy represents a burgeoning dynamic market with rapid product innovation. Currently, researchers group e-cigarette devices as belonging to one of four generations (Figure 1), reflecting changes in device models. Notably, many devices are now modifiable by users. As of 2014, 466 different e-cigarette brands and 7,000 unique e-liquid flavours were reported to have been on sale on English language internet sites.[3] Hsu *et al*. updated the inventory of websites in 2016-2017 and they reported that 178 (38%) of the 466 brands identified in the 2013-2014 survey were no longer in operation as of July 2016, while 288 (62%) brands were still available. The authors identified 145 additional brands giving a total of 433 brands in 2017.[4] In addition, they report that the number of flavourings more than doubled to 15,586 flavours.[4]

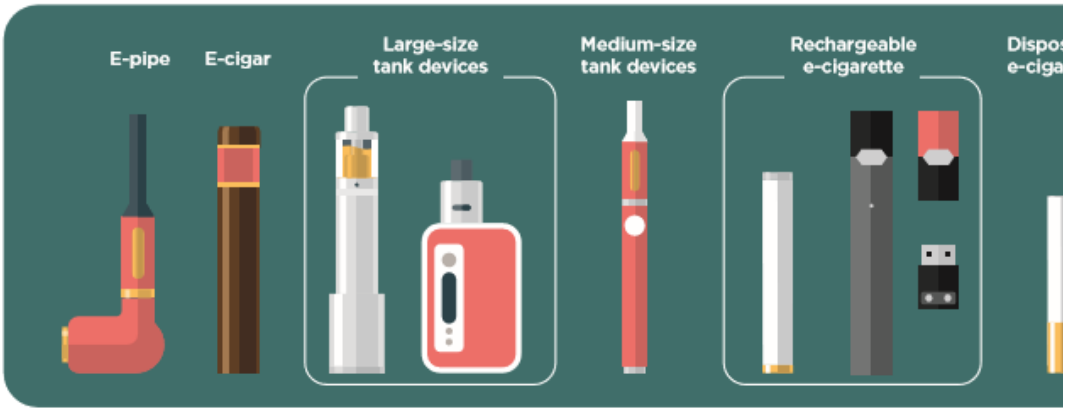


Figure 1 Examples of e-cigarettes currently available on the market e-cigarettes

(Image reproduced from the National Institute on Drug Abuse)[5]

2.1.1 E-cigarette characteristics

E-cigarettes are battery-operated devices with an element and a liquid-containing reservoir that is heated to allow people to inhale an aerosol. The aerosol arising from the carrier solvents (humectants) typically (although not always) contains nicotine, flavourings, and other chemicals. Other terms used to identify e-cigarettes include e-vaporisers, or electronic nicotine delivery systems (ENDS), e-hookahs, hookah pens, vapers, vape pens, and mods (short for modifiable devices). Mods are customisable e-cigarettes and contain more powerful vaporisers than earlier e-cigarette models. Although there are variations in the appearance of e-cigarettes, the National Institute on Drug Abuse has reported that regardless of their design and appearance, the devices generally operate in a similar manner and are made of similar components.[5]

E-cigarettes can resemble conventional tobacco cigarettes (cig-a-likes), cigars, or pipes. However, they can also resemble everyday items such as pens and USB memory sticks or they can be designed to appeal to specific sub-groups and cultural identities.

The primary components of e-cigarette are:

- A cartridge or reservoir, which holds a liquid solution (e-liquid or e-juice) containing varying amounts of nicotine, flavourings, and other chemicals
- A heating element (atomiser or cartomisers)
- A power source (usually a battery)
- A mouthpiece that the person uses to inhale

In many e-cigarettes, puffing activates the battery-powered heating device, which vaporises the liquid in the cartridge.[5]

2.1.2 E-cigarette liquids

The Academies of Sciences have stated that the types and concentrations of chemical constituents produced in the e-cigarette vapour depend not just on the formulation and flavour of the e-liquid but also on the voltage used.[6] There are thousands of e-liquid brands available; coupled with the rate of market expansion and the time required to study the impact of individual products, a systematic understanding of the chemical contents of the aerosols arising from different brands and their relationship with health outcomes is not yet available.

The Health and Medicine Division of the Academies of Sciences [6] has identified e-cigarettes and e-liquids as having the following constituents:

- Humectants (delivery solvents usually propylene glycol and vegetable glycerine)
- Flavourings
- Carbonyl compounds including dicarbonyls and hydroxycarbonyls
- Minor tobacco alkaloids
- Free radicals and reactive oxygen species
- Tobacco-specific nitrosamines
- Other toxicants such as volatile organic compounds, polycyclic aromatic carbons,
- Metals

2.1.3 E-cigarette carrier compounds

The Academies of Sciences' publication, *Public Health Consequences of E-Cigarettes*,[6] citing other authors, reported that most e-cigarette solvents have been reported to contain propylene glycol and glycerol as the carrier compounds, but newer products are reported to contain a nicotine base and a weak organic acid that forms a nicotine salt. The Academies of Sciences stated that these devices are patterned after technology described by Rose *et al*.(2008). These nicotine salt forming products, JUUL™ by JUUL Labs and P3L by Philip Morris Products, have reported chemical compositions as follows. The JUUL™ pods (i.e. prefilled cartridges) contain benzoic acid and nicotine in a 0.97–1 molar concentration ratio, indicating that benzoic acid is a major ingredient of this device. The nicotine salt (nicotine benzoate) forms when the device is activated and is delivered to the user in an aerosol form. The P3L stores its nicotine base and lactic acid in separate cavities, which on activation and controlled heating, release the nicotine salt (nicotine lactate) as an aerosol. Both products indicate the potential use of nicotine salts to deliver nicotine. In addition to variations in chemical composition arising from the constituent parts of e-liquid and voltage strength, distinctions in sensory perceptions, both of feeling and taste, arise from e-liquid constituent variations. Propylene glycol, thinner than glycerol, has been reported to have a better 'throat hit' than glycerol and to better carry flavour, while glycerol

is reported to be 'smoother' than propylene glycol. These are all factors which influence the appeal of specific e-cigarettes.[6]

2.1.4 Flavourings

There were 7,764 unique e-liquid flavours identified as available to e-cigarette users as of 2014.[3] In Hsu *et al.* published update in 2016-2017, they report that the number of flavourings more than doubled to 15,586 flavours.[4] Little is known about the health implications of their presence. The Academies of Sciences publication, Public Health Consequences of E-Cigarettes,[6] citing other authors, reported that flavouring components are often not included in the ingredient lists of e-cigarette products. According to the Academies of Sciences, the United States Flavor and Extract Manufacturers Association considers many flavours as being generally safe in food products for ingestion and at recommended levels of intended use, but these ingredients are not safety-tested for exposure routes such as inhalation. Therefore, the effects of these chemicals when aerosolised and inhaled is not known.

2.1.5 Nicotine intake and absorption

The Academies of Sciences' report *Public Health Consequences of E-Cigarettes*[6] included an overview of nicotine intake and absorption based on the findings of four research studies. They reported that nicotine makes up approximately 95% of the alkaloid content of conventional tobacco cigarettes and 1.5% by weight in cigarette tobacco.[6] The nicotine content of commercially available e-liquids varies from low to high – it is commonly 0.3–5% by volume.

The Academies of Sciences reported that following e-cigarette activation, nicotine is released from the e-liquid on the aerosol particles and inhaled.[6] The Academies of Sciences, based on Benowitz 2009, described the process by which nicotine bound to particles drawn into the mouth and upper airways is absorbed into the circulation and even more rapidly absorbed into the pulmonary venous circulation as the particles reach the lungs. Absorption in the mouth and upper airways is thought to account for the sensory effects of nicotine in the mouth and throat. Following nicotine entry into the circulation, it passes into the arterial circulation and moves across the blood–brain barrier into the brain, diffusing readily in brain tissue and binding stereoselectively with nicotinic cholinergic receptors. This release of multiple neurotransmitters in the brain generates dopamine, which is related to nicotine's pharmacodynamics associated with pleasure and appetite suppression, in the mesolimbic area, the frontal cortex, and the corpus striatum. The pleasurable dopamine effect is regarded as a critical role in nicotine's reinforcing effects. Other nicotine-induced behaviours are mediated by a variety of neurotransmitters that are also released, including norepinephrine (arousal, appetite suppression), acetylcholine (arousal, cognitive enhancement), serotonin (mood modulation, appetite suppression), gamma-aminobutyric acid (reduction of anxiety and tension), glutamate (learning, memory enhancement), and endorphins (reduction of anxiety and tension).[6]

The Academies of Sciences' publication, *Public Health Consequences of E-Cigarettes*,[6] based on two research studies, also reported that nicotine addiction develops as a neurobiological adaptation to chronic nicotine exposure. One nicotine dependence characteristic is the emergence of withdrawal symptoms on abrupt cessation of nicotine administration. Tolerance (neuroadaptation) to nicotine develops for some nicotinic effects on repeated exposure to nicotine. The number of nicotinic cholinergic receptors binding sites in the brain increases, which is thought to represent upregulation in the response of nicotine-mediated desensitisation of receptors. During periods of abstinence in chronic smokers, such as during night-time sleep, previously desensitised a4b2 nicotinic cholinergic receptors become unoccupied and recover to a responsive state. Abstinence symptoms are believed to develop when these nicotinic cholinergic receptors revert to this unoccupied and responsive state. Craving and withdrawal symptoms are alleviated through nicotine binding and desensitisation of the receptors. Stimulation of these globally expressed nicotinic cholinergic receptors causes wide-ranging physiological effects such as nicotine intoxication syndrome. Symptoms of nicotine intoxication syndrome include nausea and vomiting. More severe poisoning can progress to diarrhoea, increased salivation and respiratory secretions, bradycardia, seizures, and respiratory depression. The rapid development of tolerance to nicotine with repeated administration helps counter the development of acute nicotine toxicity.[6]

2.1.6 Pharmacokinetics and pharmacodynamics of nicotine

In the *Public Health Consequences of E-Cigarettes*, the Academies of Sciences completed an overview of the pharmacokinetics and pharmacodynamics of nicotine by synthesising the findings of 10 research studies.[6] They reported that the amount and mode of nicotine intake influences the addictiveness of a tobacco product. The abuse liability of tobacco products increases with higher delivery, faster rate of absorption, and higher blood nicotine concentrations. The dose and route of administration influences the release of nicotine in the brain and thus the pharmacological effects. Nicotine in tobacco smoke is rapidly absorbed into the pulmonary venous circulation once it reaches the small airways and alveolar region of the lungs, progressing to the left ventricle of the heart, the systemic arterial circulation, and finally the brain. High levels of nicotine reach the brain approximately 15 seconds after a puff on a conventional cigarette. This rapid increase in nicotine levels in the brain leads to activation of the dopaminergic reward system, producing rapid behavioural reinforcement. This therefore makes smoking, over products such as patches and gums, the most reinforcing and dependence-producing form of nicotine administration.[6]

From a review of literature, the Academies of Sciences found that nicotine delivery from e-cigarettes through the pulmonary route is similar to delivery via conventional tobacco cigarettes and has a similar plasma nicotine profile.[6] This potential high and rapid nicotine delivery can be expected to produce nicotine-related psychoactive effects that can cause or maintain nicotine dependence. The receptor-binding capacity of nicotine in the brain is higher in smokers compared with non-smokers, due to the upregulation of nicotinic cholinergic receptors in the brains of smokers. Nicotine is rapidly delivered and absorbed when smoking, and as such, blood nicotine concentration rises while smoking and peaks at the end of smoking. Nicotine levels decline rapidly during the 20 minutes following smoking as nicotine distributes to tissue, with a distribution half-life of 8 minutes. The elimination half-life of nicotine is approximately 2 hours. Thus, nicotine from regular smoking accumulates in the body during waking hours. Therefore, while smoking results in exposure to nicotine in an intermittent and transient manner, exposure lasts 24 hours per day. Exposure leads to the persistent presence of nicotine in the brain, with resulting structural and functional changes in nicotinic receptors and in the intracellular processes of neuroadaptation.[6]

2.1.7 Metals

The Academies of Sciences' publication, *Public Health Consequences of E-Cigarettes*,[6] identified eight studies reporting on toxic metals in e-liquid emissions, including lead, nickel, and chromium. The report also noted that toxic metals may originate from any of several parts of an e-cigarette device. This includes the metallic coil that heats the e-liquid to produce the aerosol inhaled by the user, as well as seams and wires in the devices. Alloys found in e-cigarettes include kanthal, which contains aluminium, chromium, and iron; Ni-200, made of nickel; and nichrome, which comprises chromium and nickel. Furthermore, metals such as tin have been found in the joints or seams. Aside from the metals in the device itself, e-liquids may also contain metals, and some e-liquid solutions have been reported to contain arsenic.[6]

2.2 Heat-not-burn tobacco products

The aim of the background section is to provide an understanding of heat-not-burn tobacco products.

2.2.1 Product types

Heat-not-burn devices appear to have arrived on the American market in 1988, when R. J. Reynolds introduced the Premier™.[7] This product was later withdrawn. A related product, the Eclipse, was test-marketed in 1996 and reintroduced with a modified filter in 1997.[8] Since then, several other brands have been successfully introduced to the market. The WHO heated tobacco products (also known as heat-not-burn devices) market monitoring information sheet[9] notes that early versions of heat-not-burn devices were developed in the early 1980s, and that the three main manufacturers in this sector are Philip Morris International, Japan Tobacco International and British American Tobacco. It is also noted in this 2018 document that sales figures for heated tobacco products were expected to reach US $ 17.9 billion by 2021.[9]

The earlier versions of heat-not-burn devices were developed further and results in many variations on the design (Table 1). The iQOS, developed by Philip Morris International, was launched in 2014 in Japan[10] and by 2018 was available in 35 countries.[9] Caputi notes that iQOS had captured 2.4% of Tokyo's market share for tobacco within 6 months of release.[11] Other examples of these product types include glo by British American Tobacco, launched in Japan in 2016, [12] and ModelOne, released by Ploom in 2010.[13] Ploom later became Pax Labs. Ploom vaporisers, by Japan Tobacco International, were originally introduced in 2013[14] and are considered to be loose-leaf tobacco vaporisers,[15] while Ploom Tech, also by Japan Tobacco International were launched in 2016.[16] The Korea Tobacco and Ginseng Corporation put lil on the market in 2017.[17] Imperial Brands launched a heat-not-burn device (Pulze) in Japan in 2019.[18]

Lopez (2016) notes that there has been much less study of heat-not-burn devices than there has of e-cigarettes.[15]

Table 1 Heat-not-burn tobacco product types, manufacturer, and year of launch

Product	Manufacturer	Year launched
ModelOne	Ploom (later Pax Labs)	2010
Ploom vaporizers	Japan Tobacco International	2013
IQOS	Philip Morris International	2014
glo iFuse	British American Tobacco	2015
Ploom tech	Japan Tobacco International	2016
glo	British American Tobacco	2016
lil	Korea Tobacco & Ginseng Corporation	2017
TEEPS	Philip Morris International	2017
Pulze	Imperial Brands	2019

2.2.2 Product characteristics

The primary characteristic of the heat-not-burn device is that the tobacco in the device is heated, rather than undergoing combustion. The Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment describe three basic types of heat-not-burn mechanisms.[19] These are:

- Direct heating of processed tobacco to produce a vapour,
- Heating of processed tobacco in a vaporiser, and
- Passing of vapour (from non-tobacco sources) over processed tobacco in order to give the vapour a flavour.

Mallock *et al.* (2019) notes that while in typical cigarettes, combustion takes place at 700-950°C, in heat-not-burn devices heating of up to 350°C results in vapour or aerosol.[20]. The temperature of the stick is controlled at 150-350° C without combustion, fire, ash, or smoke (Figure 2).[20] Direct heating of the tobacco may be carried out by heating disposable tobacco sticks via a thin metallic blade.

The heat-not-burn tobacco product comprises three components, each with a different function. These are the tobacco stick, a pen-like heater (or holder) and the charger. The tobacco stick, which contains processed tobacco, is inserted in the holder and is heated by a controlled electrical element energised by a charge. The emissions are inhaled via a mouthpiece. In their review, Dautzenberg and Dautzenberg[21] noted that some devices were time-limited – the user was required to inhale within a set period (often 3.5 minutes to 10 minutes) before the device would automatically turn off. This was designed, they state, to maintain peaks of nicotine and upregulate nicotinic receptors.

In contrast to e-cigarettes, heat-not-burn tobacco products do not vaporise liquid-containing flavourings, propylene glycol, or vegetable glycerol.[22] In contrast to conventional tobacco cigarettes, heat-not-burn tobacco products heat, rather than burn, tobacco and thus are purported to be less harmful to health than conventional tobacco cigarettes.

To date, independent reporting on the constituent properties of heat-not-burn tobacco products do not seem to be available, although Simonavicius[23] notes the preparation of a review by committees advising the UK government which excluded research funded by producers of heat-not-burn devices.[19] However, analysis of contents of smoke from heat-not-burn tobacco products compared with that of conventional tobacco cigarettes reported a range of volatile organic compounds (such as acetaldehyde, acetone, acroleine, benzaldehyde, crotonaldehyde, formaldehyde, isovaleraldehyde), polycyclic aromatic hydrocarbons (such as naphthalene, acenaphthylene, acenaphthene, fluorene) and inorganic compounds (such as nitric oxide) in the mainstream smoked. [24]

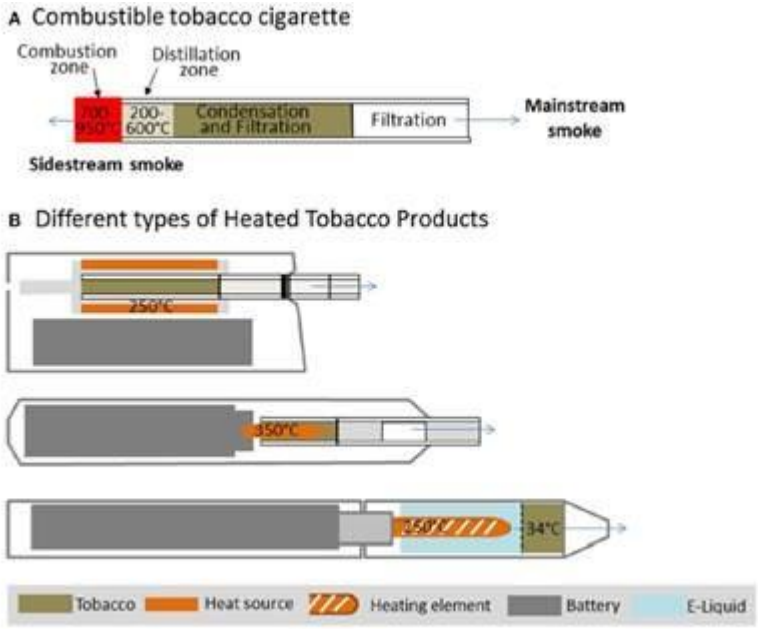


Figure 2 Conventional cigarette temperature versus 3 types of heat-not-burn products with their peak temperatures

(Image reproduced from Mallock et al.[20])

2.3 Regulation of e-cigarettes and heat-not-burn products

2.3.1 Europe

In February 2014, the European Parliament approved new regulations for tobacco products, including e-cigarettes, prohibiting the sale of e-cigarettes to persons under 18 years.[25] The Tobacco Products Directive (2014/40/EU) was issued on 19 May 2014 and became applicable in European Union (EU) countries on 20 May 2016. The Directive lays down rules governing the manufacture, presentation and sale of tobacco and related products including e-cigarettes. In addition to prohibiting sales to persons under 18 years, Article 20 of the new regulations which prohibit promotional elements on e-cigarette packaging, and cross-border advertising and promotion of e-cigarettes, sets limits on maximum concentrations of nicotine in liquids, limits maximum volumes of liquid that can be sold in a single container, requires childproof and tamper-proof packaging of liquid, sets requirements on purity of ingredients, requires that the devices deliver consistent doses of vapour, requires disclosure of ingredients and nicotine content, and allows member state regulators to act if the regulations are violated. In addition, warning labels can be placed on e-cigarettes. The regulations do not ban vaping in public places.[25]

2.3.2 Ireland

According to the Health Services Executive website, the Minister for Health in Ireland signed the Regulations transposing the EU Tobacco Products Directive into Irish law.[26] On 20 May 2016, the European Union (Manufacture, Presentation and Sale of Tobacco and Related Products) Regulations

2016 (S.I. No. 271 of 2016) (with Part 5 on electronic cigarettes and herbal products for smoking) came into force and, in September 2018, the amended Regulations (S.I. No. 365 of 2018)(with regulations on the sale of e-liquids) came into effect.[26] In addition, Ireland is in the process of enacting legislation to license retailers of e-cigarettes and introducing a minimum age of sale of 18 years.

Manufacturers and importers of tobacco products, e- cigarettes, refill containers, and other tobacco-related products must apply for permission to market their products by submitting key information on the nature of these products to authorities in the Member States of the European Union.[26] In a personal communication to the research team, the Revenue Commissioners (in Ireland) reported that applications for the marketing of e-cigarettes have been made and approved, but to date, no heat-not-burn tobacco products have been authorised for sale in Ireland. [Personal correspondence, Revenue Commissioners Ireland Date and European Union, April 2020]. Ireland's Revenue Commissions also state that its systems do not record data on the brands of e-cigarette retailed in Ireland. With respect to e-cigarettes, there is no independent overview of brands sold in Ireland.

This mapping exercise presents findings from peer review journal articles. The findings relate to the product(s) examined in these papers. These findings may not apply to other e-cigarette or heat-not-burn products unless the other products have the exact same chemical composition and/or the device has the same design.

2.4 Research needs

Given the relatively short time that e-cigarettes have been in use, the evidence base regarding their effects is limited. In 2015, The Academies of Sciences' publication,[6] citing Walton *et al*.(2015) reported that there was enormous need for more evidence on e-cigarette devices, constituents, and exposures.

Heat-not-burn tobacco products have been in use since 1988 and only a small range of the marketed products have been evaluated in peer reviewed published articles. Most published articles are authored by industry and provide an incomplete assessment of their impact on health outcomes compared to conventional tobacco cigarettes or non-smokers. In addition, there are limitations regarding the generalisability of findings on these products due to differences between products.

This research project sought to map the current available English language research on e-cigarettes and heat-not-burn tobacco products in humans, aligning the findings with the identified areas of interest to provide a high-level overview of the current state of play in this field.

3 Methods

3.1 Conceptual methods and coding framework

Mapping exercises provide an overview of the nature and extent of the available evidence, with limited description of the data. A standard systematic search approach was used for this programme of research including the mapping exercise. Published studies and other material were sourced via database and supplemental searches. Articles were double-screened until a final core set of relevant articles that would speak to the five research questions in Section 1.1 was agreed upon.

The information to answer the two questions pertaining to this mapping exercise, the harms and benefits of e-cigarettes and heat-not-burn tobacco products, was identified in a variety of epidemiological study designs, including case reports, case series, cross-sectional surveys, case-control studies, longitudinal cohort studies, and interventional trials (with the addition of surveillance reports).[27] These study designs are used to outline the differing levels of evidence in existing research (Figure 3). The purpose of coding the included papers by epidemiological study design was to allow readers consider each article taking account of the strengths and limitations of the study design employed to complete the research. Descriptive study designs are useful to describe health outcomes by person, place, and time, while observational studies are useful for identifying associations between exposure and outcomes. Randomised control trials are useful to determine the incidence of outcomes in an intervention group compared to a control or gold standard intervention group. Under certain conditions, randomised control trials are said to provide the highest level of evidence in primary research studies and may meet the criteria for causality. The Bradford-Hill criteria for causality are: strength of association or effect size, consistency of findings across studies known as reproducibility, biological credibility (plausibility), specificity (other explanations), a temporal relationship (exposure occurred before the outcome) and biological gradient known as a dose-response relationship, coherence (consistent with other lines of evidence); and analogy (similar agents act similarly).[28]

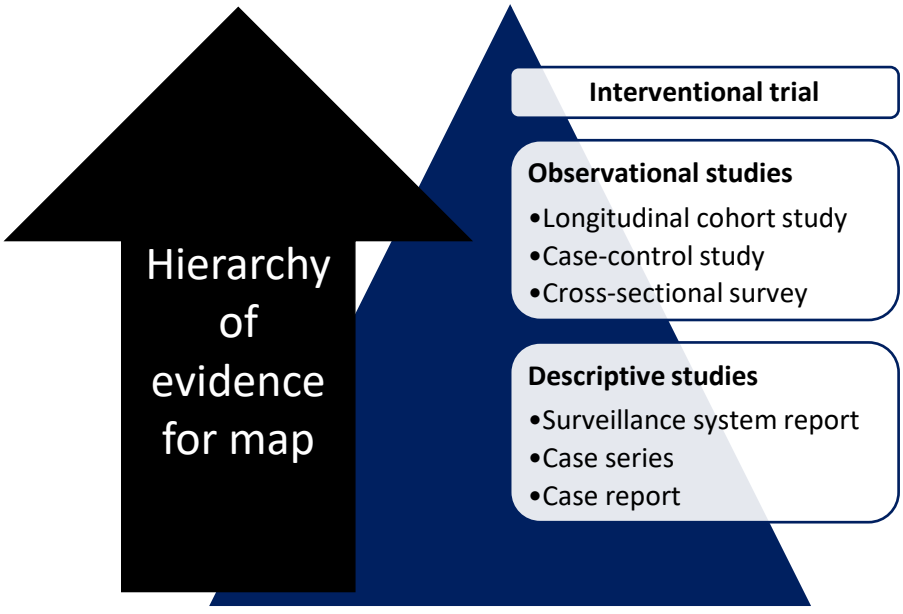


Figure 3 Hierarchy of evidence employed in mapping exercise

As the number of articles (n=6510) found was extensive, it was decided to map the data by study design and then by outcome (harm, benefit, or outcome measurement) in order to give an accurate picture of current evidence for the possible harms and benefits of e-cigarettes and heat-not-burn tobacco products (Figures 3 and 4).

Following examination of the full text papers, the lead researcher (AMcC) noted that there was a wide array of reported outcomes which included: clinical pathological outcomes (such as injuries, poisoning and respiratory diseases), biological markers of health (such as heart rate, blood pressure,

cholesterol), organ functionality (such as forced vital capacity, forced expiratory volume in the first second, and forced expiratory ratio) and measures of chemical toxicity (such as carbon monoxide, nicotine, metals, volatile organic compounds, tobacco-specific smoking-related carcinogens). The health outcomes would need to be categorised using an acceptable coding framework. Coding frameworks for the various measures of, or influences on, health include volumes such as the International Classification of Diseases (ICD)[29] and the Medical Dictionary for Regulatory Activities (MedDRA Medical Coding).[30] These coding frameworks were considered, but the time requirement to code the identified outcomes would be prohibitive. Google searches were undertaken to identify if other reporting frameworks had been adopted or advocated taking account of the observed diversity of findings. Websites of the World Health Organization, federal-level health and regulatory organisations of Australia, Canada and the United States of America (USA), the European Union (EU) and the United Kingdom (UK) were searched. AMcC identified the *Public Health Consequences of E-Cigarettes* by the Academies of Sciences in the USA as a viable reporting framework.[6] Outcomes arising from smoking conventional tobacco cigarettes and other nicotine products can be grouped under umbrella terms identified by the Academies of Sciences: dependence and abuse liability; cardiovascular diseases; cancers; respiratory diseases; oral diseases; developmental and reproductive effects; and injuries and poisonings.[6] The authors of this mapping exercise added two further headings – exposure to e-cigarette toxins; and other outcomes – in order to categorise literature that did not align under the existing headings. Harms and benefits could be the result of either use of, or exposure to, e-cigarettes or e-liquid or heat-not-burn tobacco products (Figure 4).

Figure 4 Adapted Academies of Sciences' framework

3.2 Inclusion and exclusion criteria

The identification of the public health harms and benefits of e-cigarettes and heat-not-burn products required inclusion of quantitative epidemiological studies on the human population specifically case reports, case series, cross-sectional surveys, case-control studies, longitudinal cohort studies, and interventional trials. One additional publication type, surveillance reports, which did not fit within the classic epidemiologic study design framework were included in this work. Surveillance reports, disseminated findings from the systematic collection and analysis of health events, allow for planning, implementation, and evaluation of public health programmes. They provide a picture on the current incidence of events which merit a public health appraisal to identify possible harms or benefits if e-cigarettes.

Publication types to be excluded were:

- Letters (except for primary study-type letters)
- Systematic reviews
- Meeting abstracts
- Summary reviews and commentaries, and
- Review and study protocols.

Study types and topics to be excluded were:

- News items
- Editorials
- Validation of diagnostic tests
- Animal studies
- *In vitro* papers
- Cell line studies
- Chemistry
- Articles on puffing topography
- Drug-taking using e-cigarette devices
- Development of biomarker measurement
- Measurement of nicotine levels in non-clinical studies on the devices used
- Occupational safety standards
- Regulation of devices
- User perceptions
- Studies on taste (without harms)
- Prevalence
- Marketing
- Economics, and
- Modelling.

The date limits used were 2005–2019 for e-cigarettes and 1988–2019 for heat-not-burn tobacco products (reflecting their respective introduction dates). While versions of these products had been introduced at different timepoints, these are considered the introduction dates for the products as they are currently understood.

No language limit was imposed initially (apart from the implicit limit of using databases that index primarily English-language research). However, on immersion in the full extent of the topic, it became clear that a rudimentary translation of non-English-language articles would not be adequate to understand such technical material and there would not be time or resources to have all the non-English results translated professionally within the time limit of the review. Thus, reluctantly, non-English language articles were screened out from the articles put forward for full analysis. However,

the authors are aware that a body of research published in other languages exists which could add to the body of literature being mapped.

Where duplicate articles occurred, only one of the two articles was included. Despite 'deduplicating' the articles prior to screening, some duplicates were noted at 'title and abstract' and at full-text screening stages. These are likely to have got through the deduplication process due to inaccurate or incomplete information in some of the search fields, for example, wrong or missing titles or authors, missing digital object identifiers, or other information types.

Table 2 presents the population, intervention (or exposure), comparator, or outcome (PICO) for the two questions regarding the benefits and harms of e-cigarettes and heat-not-burn tobacco products answered in this mapping exercise.

Table 2 Population, intervention (exposure), comparator, or outcome for mapping exercise

Question	E-cigarettes benefits and harms	Heat-not-burn tobacco products benefits and harms
Population	All human subjects	All human subjects
Intervention or exposure	E-cigarettes	Heat-not-burn tobacco products
Comparator	None/any, including other e-cigarette users with and without nicotine, conventional combustible tobacco cigarette smokers, non-smokers	None/any, including other e-cigarette users with and without nicotine, conventional combustible tobacco cigarette smokers, non-smokers
Outcome	Any public benefits or medical harms to individuals or the population, including clinical pathology (disease and injury) and/or measures of organ function, levels of toxicants	Any public benefits or medical harms to individuals or the population, including clinical pathology (disease and injury) and/or measures of organ function, levels of toxicants
Study type	All epidemiology study types and surveillance system related papers	All epidemiology study types and surveillance systems
Exclusion criteria post-screening	Non-English-language articles	Non-English-language articles
Search dates	2005–2019	1988–2019

We defined public health harms as both clinically diagnosed pathological outcomes (diagnosis of disease or injury) and damage or an injury to biological tissue that can have a short- or long-term outcome, leading to disease.

We defined public health benefits as when a substance, or activity improves health.

Harms and benefits could be the result of either use of, or exposure to, e-cigarettes or e-liquid or heat-not- burn products.

3.3 Information searches

Following scoping searches in late March 2019 using Ovid MEDLINE and Ovid PsycINFO, and the search engine Google, a search plan was designed by the information specialist (CL) to capture relevant studies and other data. The plan included literature searches using bibliographic databases, registries, repositories, and search engines. Supplemental searches were planned and carried out, including forward and backward citation searching of recent systematic reviews and authoritative reports. Follow-up searches of Ovid MEDLINE were scheduled to be carried out after the initial main search in order to maintain currency of the mapping exercise.

The initial database searches were carried out from 4 to 10 April 2019. These results were combined using EndNote X7, and were uploaded to EPPI-Reviewer 4 (V. 4.11.0.0).[31] Subsequent supplemental searches were carried out in August, October, and November 2019. In the subsequent supplementary database searches, due to resource constraints, searching was limited to Ovid MEDLINE.

3.3.1 Bibliographic databases

The primary database searches were carried out in April 2019. The databases included were:

- Ovid MEDLINE (Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to April 12, 2019)
- Elsevier Embase
- Ovid PsycINFO
- Wiley Cochrane Database of Systematic Reviews
- Wiley Cochrane Central Register of Controlled Trials
- PAHO/WHO/Bireme LILACS (including the databases LILACS, IBECS, CUMED, BDENF – Nursing, BBO – Dentistry, WHO IRIS, PAHO IRIS, Index Psychology – Scientific journals and MedCarib), and
- PROSPERO international prospective register for systematic reviews (Centre for Reviews and Dissemination, University of York).
- Search engine: Google Scholar

Peer review of the search strategy by another information specialist, as recommended in the PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement,[32] was not carried out, as resources were unavailable when conducting the searches. However, every effort was made by the information specialist to critically appraise the search strategies using the checklist outlined in the PRESS guidelines in order to follow the PRESS recommendations. The results of the April 2019 search were screened for inclusion by two researchers (AMcC and DOB) and the information specialist (CL).

In August 2019, a two-part supplemental search was carried out. This included a literature search using Ovid MEDLINE (with the same search terms as the original search but limited to recent articles), and a citation search based on core reviews and reports. The list of reports and reviews used for this search is included in Appendix 1. The review titles were sourced by combining the Ovid MEDLINE e-cigarette and heat-not-burn tobacco product searches with a customised version of the Ovid Expert Searches systematic review filter and then limiting them to publications from the previous five years. The titles were screened for clinical relevance in accordance with PICO (e.g. smoking cessation, harms, benefits, and initiation) by the information specialist (CL), and titles were confirmed for inclusion with the lead author (AMcC). The results from these searches were added to EndNote X7 and screened initially for duplicates, then for relevance using the PICO mapping exercise (Table 2), and then for originality (whether they were already included in the original search results).

Further simple supplemental searches were carried out on the 11th October 2019 and the 18th November 2019 using Ovid MEDLINE, with the same search terms as before. The results were screened initially by the information specialist to eliminate articles that had already been screened in other searches, and to eliminate highly irrelevant articles (e.g. articles not relating to e-cigarettes or heat-not-burn tobacco products). The remaining results were screened by the lead researcher (AMcC) and any relevant articles were retained.

The full search strategies used in the initial searches of Ovid MEDLINE and other databases are included in Appendix 1. The MEDLINE searches used in the supplemental searches were the same as the initial MEDLINE strategy.

The searches were robust and comprehensive but not exhaustive. The use of journal hand-searching, follow-up of relevant authors, and more exhaustive searches of other databases were considered for

this mapping exercise, but due to time considerations, it was not possible to incorporate all these methods in this project.

3.3.2 Keywords

Keywords for these searches were compiled from scoping searches on the topic carried out in MEDLINE and Google, and with the assistance of PubMed PubReMiner,[33] the PubMed text-mining software. This software allowed the easy capture of relevant medical subject headings (MeSH) terms.

The keywords used in building the searches were based on variations of terms for e-cigarette and heat-not-burn tobacco products, for example, e-cig*, e-liquid, vape, vaping, cigalike, HnB [heat-not-burn tobacco products], heatsticks, electronic nicotine delivery system (ENDS), and electronic non-nicotine delivery. Non-English terms for these concepts were also included, for example, e-sigaret*, E-Zigarette, and e-papieros. Some high-profile brand names, such as JUUL and IQOS, were included.

For databases with a controlled vocabulary, such as MEDLINE, Cochrane, PsycINFO, PROSPERO, and Embase, terms from the relevant thesaurus (e.g. MeSH, Emtree, PsycINFO Thesaurus) were also incorporated.

Given the considerable body of literature published to date mentioning e-cigarettes and heat-not-burn tobacco products and the limited amount of time available to complete this mapping exercise, additional search terms were used to broadly exclude some categories of study, for example, MeSH and free terms for animal studies and cell line studies.

Rather than split the single e-cigarette/heat-not-burn tobacco products search into three separate searches for smoking cessation, harms and benefits, and initiation studies, a single search was used for all three subtopics, and results were filtered via the screening process to the appropriate subtopic. It was anticipated that several results would be relevant to more than one question.

3.3.3 Grey literature

To increase the opportunity to capture as much relevant data as possible, it was decided to include CORE (Core.ac.uk) and Google Scholar in the search plan. CORE is an open access research repository and Google Scholar is a search engine which primarily includes scholarly publications. The search strategies used with these resources were very much simplified and reduced, relative to the extended search strategies possible with Ovid MEDLINE or PsycINFO.

Some grey literature was also included with the supplemental citation search of reviews and reports carried out in August 2019 and outlined above.

3.3.4 Screening

A comprehensive screening process was carried out. Results (n=6,510 after deduplication) from the literature searches were exported to EPPI-Reviewer 4. Title/abstract screening was carried out by two researchers (AMcC and DOB) and the information specialist (CL). A pilot group consisting of 10% of the results was initially screened to test the screening questions and process. The remainder of the results was then screened using the same criteria. The screening questions comprised the five research questions inclusion and exclusion criteria (see Section 1.2 and Section 3.3). Where there was doubt about the relevance of an article, it was included for the next round of screening.

For the mapping exercise, inclusion and exclusion criteria for the title and abstract screening process were those outlined in Section 3.3 and Table 2. A more limited set of terms were used for heat-not-burn tobacco products such as HnB and heatsticks.

After the title/abstract stage of screening, 526 papers relating to harms and benefits of e-cigarettes were retained, while 25 papers relating to heat-not-burn devices were retained; this gave 551 papers in total. The full texts of the relevant 551 papers were sourced and then screened to answer specific inclusion queries that could not be answered using the published abstracts alone. This stage of screening was carried out by two researchers (AMcC and DOB), using the same inclusion and exclusion criteria in Section 3.3 and Table 2. One hundred and eighty-two articles were excluded on close reading. After this preliminary full text screening, 369 papers were carried forward to the full-

text reading stage – 339 papers relating to e-cigarettes and 30 papers relating to heat-not-burn devices. The main reason for exclusion was details of study design or methods were unclear. Five papers were re-assigned from the e-cigarette category to the heat-not-burn tobacco product category, bringing this total up to 30 papers.

Title/abstract screening of the outputs of the three supplemental searches (these are described in Section 3.4.1) was carried out by the information specialist to eliminate any obviously out-of-scope results. Potentially relevant results were then screened by one researcher (AMcC). From the 110 supplemental results relating to e-cigarette and heat-not-burn tobacco product harms and benefits retrieved over the three searches, 96 additional relevant results were retrieved, all of which pertained to e-cigarettes. These were added to the 369 papers (e-cigarettes: N=339 and heat-not-burn products: N=30) remaining after full text screening (e-cigarettes: N=435 and heat-not-burn products: N=30)). Following full text screening, 77 papers were excluded at this stage and one paper had to be reclassified from one question to another. The screening process resulted in a total of 388 papers eligible for inclusion in the final mapping exercise. Of this total, 361 papers dealt with the topic of e-cigarettes and 28 papers covered heat-not-burn devices, with one paper[1] dealing with both types of devices and included in both categories. The results of the search and screening process is outlined in the PRISMA flow chart in Figure 5 in Section 4.1.

3.4 Data extraction

The initial plan was to complete a systematic review of the health-related benefits and harms of e-cigarettes and heat-not-burn tobacco products, but in September, it emerged that the number of papers for inclusion would be circa 370 primary epidemiological papers, and given the resources available to the project and the tight deadline (April 2019 to January 2020 and 1.4 FTE staff), it was decided by the unit manager (JL) to map the included primary studies on harms and benefits so as to provide the Department of Health with an indicative view of the harms and benefits of e-cigarettes and heat-not-burn products. One researcher (AMcC) extracted data from the included papers into bespoke extraction tables by study design and by Academies of Sciences categories. Data aligning with, and representative of, the following headings were extracted: author and year; main relationship or outcomes reported; age; sex; country; ethnicity; data source; study or trial duration (for the longitudinal cohort and intervention studies); population size; data collection period; e-cigarette use, smoking, and other related behaviours; actual outcomes; authors' summary conclusions; and information on the device and smoking-related products (for the observational and interventional studies). For case reports, case series and surveillance reports, we extracted: author and year; product and dose ingested; outcome; as well as age, sex, and country if the data were available. The data measures for extraction were not reported in all papers, and where data were missing, this is acknowledged in the tables in Sections 4 and 5, and in the Appendices 2-5. The data extraction was not validated by another researcher.

3.5 Quality assessment

As this is a mapping exercise, there was no quality assessment of individual primary papers required. Quality assessment normally requires the use of an appropriate validated tool to evaluate the quality of a peer review paper. The assessment tool is study design specific. Such tools allow the researcher to assess: appropriateness of the study design to answer the research question; method(s) employed to minimise biases; validity of measures of exposures and outcomes; suitability of the statistical analysis; control for confounding; and accuracy in reporting. This is a feature of mapping exercises that we have discussed in Section 6.4 of the discussion.

3.6 Literature mapping and summarisation of extracted information

A mapping exercise was completed to describe the nature and extent of the literature on harms and benefits of e-cigarettes and heat-not-burn tobacco products. A mapping exercise is a methodical review of all the published literature in a subject area. Study summaries are presented, or arranged, by headings and subheadings in order to describe, design, and develop effective research questions, and research programmes. The purpose of the work is not to quantify the relevant nature of the

impact of e-cigarettes or heat-not-burn tobacco products, but to identify possible harms, benefits, and areas for consideration.

As this is a mapping exercise, we describe the nature and extend of the literature by study design and scientific heading. In addition to normal mapping exercises, we presented a brief summary within the main body of the report which summarised the relationship as described by the primary paper authors in their concluding text. A more detailed tabulation of the primary authors self-reported findings for each paper is presented in the appendices. The heterogeneity in study findings was identified when present, but due to the nature of the mapping exercise, the potential underlying reasons for the heterogeneity were not examined.

Benefits and harms of e-cigarettes are categorised by epidemiological study design in order to assign a notional hierarchy of evidence to the literature. The HRB authors begin with descriptive epidemiological studies (case series, case reports, with the addition of surveillance studies) that are deemed to provide the lowest level of evidence. In the middle, we present observational studies (cross-sectional surveys, case-control studies, and longitudinal cohort studies) and we end with epidemiological studies that are said to provide the highest level of epidemiological evidence available in primary study papers (interventional trials). The HRB authors have included these studies in order to present a comprehensive map of the current situation. Regarding intervention trials, it should be noted that there are two approaches to allocation of the intervention: randomised and non-randomised. Randomised trials provide the highest level of epidemiological evidence available in primary study papers. In this mapping exercise, we identified the use of several trial designs including: randomised controlled trials; randomised crossover or Latin-square trials; non-randomised crossover or Latin-square trials; and non-randomised before and after studies. While we have presented trials with both types of randomisation within the same set of tables, and assigned a study design descriptor in the final column of each of the intervention study tables. We did not include systematic reviews of the literature in the map, as these would duplicate the material up to 2017. We did consider doing a review of reviews, but decided against this course of action as it is unlikely that published reviews would include material for the years 2018 and 2019. Information on the harms and benefits of e-cigarettes and heat-not-burn tobacco products is a rapidly changing field, so it is best mapped using primary studies.

The benefits and harms outcomes that were identified through this mapping exercise are presented under nine headings. Seven of these were identified by the Academies of Sciences: (i) dependence and abuse liability; (ii) cardiovascular diseases; (iii) cancers; (iv) respiratory diseases; (v) oral diseases; (vi) developmental and reproductive effects; and (vii) injuries and poisonings.[6] We added two further categories for outcomes that did not align with the Academies of Sciences' framework; these were (viii) exposure to e-cigarette toxins; and (ix) other outcomes. When we use the term conventional tobacco cigarettes in the text, we mean conventional combustible tobacco cigarettes.

The mapping exercise identified a range of papers reporting findings from surveillance systems that cover the new and emerging topic of e-cigarette and vaping associated lung injury (EVALI). We have presented these studies in Appendix 2 for the convenience of readers. The tables are summarised in text under the following four headings: clinical presentation; diagnostic criteria and technologies; development of algorithm and guidelines as diagnostic aids; and pathogenesis and disease aetiology.

3.6.1 Presentation of e-cigarette summaries

Summaries of the 361 e-cigarette articles are presented in tables, which are organised according to the nine outcome categories and by study design. Within each table, articles are organised by year (starting with the earliest) and then by ascending alphabetical order within each year, based on the lead author's surname. In some tables we have categorised the tables into subject themes. Each paper is also categorised as a potential benefit or harm. For some studies, potential harms or benefits are described relative to conventional tobacco cigarettes.

For ease of reading, we have minimised references in text. Also, we have referenced the papers included in the mapping exercise in their respective table. The information presented in the tables is primarily based on each article's abstract for case reports, case series, and surveillance studies; full-text documents for case series and surveillance reports were used to add specific information to the

text. Full-text articles were used to complete the tabular contents for observational studies and interventional studies. However, it should be noted that the authors' conclusions in the tables were taken from the authors' own summary or conclusions, using their own words.

The tables for cross-sectional surveys, longitudinal cohort studies, and interventional trials that are presented in Chapter 4 include information on each article's authors, study objectives, exposure, intervention, and summary concluding findings. For observational studies (cross-sectional and longitudinal cohort) and interventional trials, additional details are presented in Appendices 3–5. The tables in the appendices present the study objectives, participant numbers and characteristics, exposure or intervention, detailed descriptions of the e-cigarette or e-liquid used, outcomes measured, and authors' conclusions.

3.6.2 Presentation of heat-not-burn summaries

Summaries of the included heat-not-burn articles are presented in tables, which are organised by the nine outcome categories and by study design. Due to the nature of the findings on heat-not burn tobacco products, the layout of the tables in Section 5 differs from the layout used for e-cigarettes mentioned above. We observed that the trial papers included in Section 5 of the report were written by either industry- or academic-based authors, and we have organised the tables to reflect the authors' place of work. In addition, we observed in several instances that the same lead trial author reported on studies employing a very similar design and frequently testing the same product, or a close variation of it, in different geographical populations. Therefore, in order to ensure a better understanding of the relationship pattern between the exposure and the outcome, the papers by the same team of authors are grouped together by team, by product, and then listed in chronological order.

For ease of reading, we have minimised references in text. Also, we have referenced the papers included in the mapping exercise in their respective table. The information presented in the tables is primarily based on each article's abstract for case reports. Full-text articles were used to complete the tabular contents for observational studies and intervention studies. However, it should be noted that the authors' conclusions in the tables were taken from the authors' own summary or conclusions, using their own words. Papers reporting on heat-not burn-products are referenced in the text and tables. Each paper is also categorised as a possible benefit or harm. For some studies, possible harms or benefits are described relative to conventional tobacco cigarettes.

The tables for interventional trials that are presented in Chapter 5 include information on each article's authors, study objectives, exposure, intervention, and summary concluding findings. For interventional trials, additional details are presented in Appendix 6. The tables in Appendix 6 present the study objectives, participant numbers and characteristics, exposure or intervention, detailed descriptions of the heat-not-burn tobacco product used, outcomes measured, and authors' conclusions.

3.7 Reading the mapping exercise

The harm or benefit arising from e-cigarette or heat-not-burn product use is of an absolute or relative nature depending on the smoking status of the study participants and the presence of a study comparison group. In epidemiology, the population impact of health is considered from a clinical perspective (e.g. the health of persons with smoking-related behaviours). If the risk of developing a smoking-related disease (e.g. cardiovascular disease) changes in accordance with a change in product use, the risk, where a decrease is noted, may be considered to indicate an absolute or relative beneficial effect. Likewise, an increase in the risk of occurrence associated with product use may be considered to indicate an absolute or relative harm. Due to the mapping nature of the work undertaken here, we have stated the direction of effect for the observed relationships in observational and interventional studies, but not quantified the direction of effect. It is important to consider if harms or benefits from e-cigarettes or heat-not-burn tobacco products are greater or less than harms or benefits arising from the use of conventional tobacco cigarettes or other nicotine products which is defined as a relative effect. In order to help the reader identify the main comparative groups in each study, we identified six umbrella terms which reported on e-cigarette use and smoking related behaviours. We named these: (1) e-cigarettes or heat-not-burn products themselves; (2) conventional combustible tobacco cigarettes users; (3) dual or poly users of nicotine products; (4) never or non-users of nicotine products; (5) other product users; and (6) healthy controls.

4 Findings: e-cigarettes harms and benefits

4.1 Introduction: e-cigarettes

The possible benefits and harms of e-cigarettes are categorised by epidemiological study design to assign a notional hierarchy of evidence to the literature and presented in a mapping exercise in Chapter 4 as described in Sections 3.1 and 3.6. There were 361 peer reviewed papers on the harms and benefits of e-cigarettes which comprise 94 case report papers, 37 case series, 34 surveillance reports, 86 cross-sectional surveys, 2 case-control studies, 22 longitudinal cohort studies, and 86 interventional trials.

The benefits and harms outcomes that were identified through this mapping exercise are presented under nine headings described in Sections 3.1 and 3.6. There were 361 peer reviewed papers on the harms and benefits of e-cigarettes which comprise: 60 papers on possible harms or benefits of dependence and abuse liability, 32 on cardiovascular diseases, 7 on cancers, 78 on respiratory diseases, 24 on oral diseases, 2 on developmental and reproductive effects, 100 on injuries and poisonings, 28 on exposure to e-cigarette toxins, and 30 on other outcomes.

Summaries of the included articles are presented in tables, which are organised by the adapted Academies of Sciences nine outcome categories and by study design as described in Section 3.6.1.

The tables for cross-sectional surveys, longitudinal cohort studies, and interventional trials that are presented in Chapter 4 include information on each article's authors, study objectives, and summary concluding findings. For observational studies (cross-sectional and longitudinal cohort) and interventional trials, additional details are presented in Appendices 3–5. The tables in the appendices present the study objectives, participant numbers and characteristics, exposure or intervention, detailed descriptions of the e-cigarette or e-liquid used, outcomes measured, and authors' conclusions. The PRISMA flow chart for the mapping exercise is outlined in Figure 5.

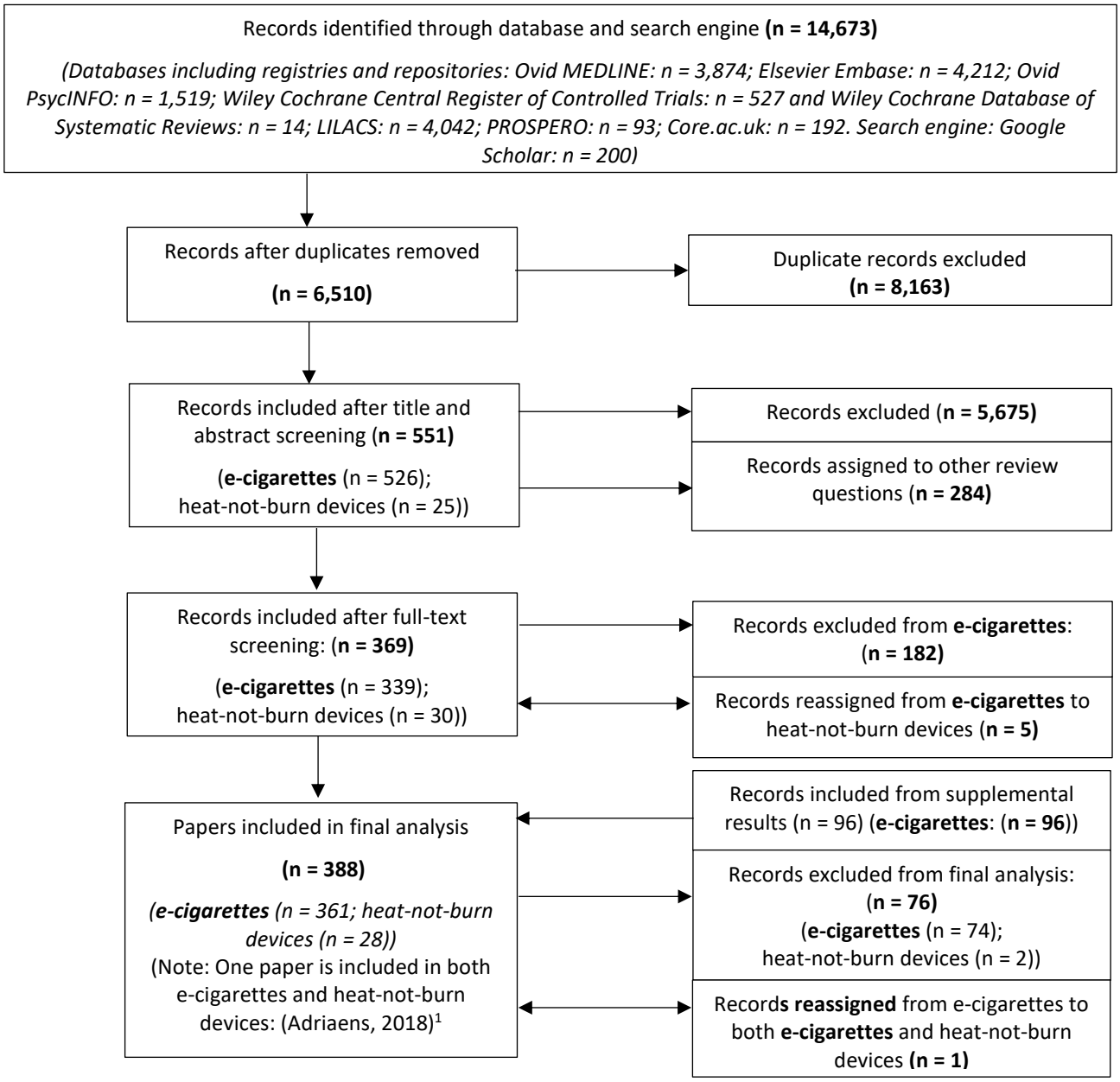


Figure 5 PRISMA flow chart

4.2 Descriptive epidemiological studies: e-cigarettes

Incidents of mainly harms and a small number of benefits associated with e-cigarette devices or e-liquid were reported in 165 papers. Stratification by research design allowed us to categorise the papers into 94 case reports, 37 case series papers, and 34 surveillance papers reporting data from information or surveillance systems.

The authors of the 94 case reports described a single hospital case of a unique event, benefit, or harm that the authors attributed to e-cigarette devices or e-liquid.[27] However, case reports can identify a hypothesis, but cannot prove causation.

The authors of the 37 case series reports described cases of similar – and medically interesting – success, morbidity, or mortality outcomes that the authors attributed to e-cigarette devices or e-liquids.[27] A case series can identify a hypothesis, but cannot prove causation.

The 34 surveillance papers reported data from information or surveillance systems to describe the geographic distribution and temporal trends in e-cigarette- and e-liquid-related harms. In some papers, incidence of harms was calculated.

4.2.1 Case reports: e-cigarettes - study characterisation, harms and benefits

The authors of the 94 case reports described a single hospital case of a unique event that they attributed to e-cigarette devices or e-liquids and resulted in a harm or a benefit (Tables 3–17). The presentation format of the case report for each paper was not standardised; some papers provided diagnosis only, other papers provided diagnosis and investigation, and the remaining papers provided diagnosis, investigation, and treatment. We did not present information on treatment in our mapping exercise, as we were focusing on describing the harms and benefits of e-cigarettes and e-liquids documented in the literature.

The 94 case reports described harms and benefits associated with e-cigarettes and e-liquids between 2012 and 2019. Overall, there were 4 case reports categorised as having a beneficial outcome and 90 case reports categorised as having a harmful outcome. Ten cases died. The sex of the cases, where reported, was 33 males and 27 females. The ages of the cases, where reported, ranged from 15 months to 66 years.

The number of case reports categorised under each of the seven umbrella headings within the adapted Academies of Sciences' framework ranged from 2 for cardiovascular diseases to 49 for injuries and poisonings; of these, 28 were injury cases and 22 were poisoning cases. Twenty-three case reports were categorised under the heading respiratory diseases (i.e. a total of 21 harms and 2 benefits); almost all harms affected the lower respiratory tract (for example, pneumonia). There were four case reports on harms categorised under the oral diseases heading, and another four harms under the exposure to e-cigarette toxins heading (for example, contact dermatitis). Twelve case reports were categorised as other outcomes. Of these case reports, two were considered benefits (for example, reduction of ulcerative colitis symptoms in one case, and reversal of blood condition in one case), and ten were considered harms (for example, affected clozapine therapeutic doses in four cases and oxygen tissue perfusion in four cases). No case reports were categorised under the headings 'cancers' or 'developmental and reproductive effects'.

4.2.1.1 Dependence and abuse liability: case reports

There were no case reports on the relationship between e-cigarettes and dependence and abuse liability outcomes.

4.2.1.2 Cardiovascular diseases: case reports

The two papers on cardiovascular outcomes reported (Table 3) the occurrence of paroxysmal atrial fibrillation in an elderly female,[34] and the development of a spontaneous coronary artery dissection in a 41-year-old breastfeeding mother 2 weeks post-delivery.[35]

Table 3 Case reports on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on cardiovascular diseases
Monroy *et al.*[34] 2012	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Paroxysmal atrial fibrillation**
Ahmed *et al.*[35] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Habitual e-cigarette smoker Outcome: **Spontaneous coronary artery dissection**

4.2.1.3 Cancers: case reports

There were no case reports on the relationship between e-cigarettes and cancers.

4.2.1.4 Respiratory diseases: case reports

The 23 papers on respiratory diseases reported findings from 12 males, 9 females, and 2 people for whom sex was not reported. The ages for males ranged from 16 to 43 years, and for females ranged from 18 to 47 years, with five females aged 42 years or over. One case died. The following diagnoses or signs and symptoms were reported for males: eosinophilic pneumonia,[36] deterioration of pulmonary function,[37] acute onset dyspnoea,[38] acute hypersensitivity pneumonitis,[39] dyspnoea and haemoptysis,[40] bronchiolitis,[41] respiratory bronchiolitis-interstitial-lung disease,[42] spontaneous pneumomediastinum,[43] recurrent spontaneous pneumothoraces, [44] and lipoid pneumonia.[45-47] Three male patients were reported to have used e-liquid containing tetrahydrocannabinol. Among females, cases of eosinophilic pneumonia,[48] dyspnoea,[49-52] multiple pulmonary nodules and liver lesions,[53] and lipoid pneumonia[54 55] were observed. A small number of patients had underlying medical conditions. Overall, 21 respiratory harms and 2 respiratory benefits were reported as a result of e-cigarette or e-liquid use (Table 4). One case of complete resolution of chronic tonsillitis and one case of resolution of chronic nasal infection in two never-smokers who had started using e-cigarettes were the only benefits reported.[56]

Table 4 Case reports on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on respiratory diseases
McCauley *et al.*[49] 2012	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Recent product use in the last seven months Outcome: **Dyspnoea, productive cough, and subjective fever**
Hureaux *et al.*[37] 2014	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Commenced vaping of either of two e-liquids both 19 mg/mL of nicotine about 25 times a day to stop smoking. Outcome: After 48 hours, an onset of cough with whitish secretions, and subsequent development of progressive breathlessness on minimal exertion over a period of one-week giving rise to **bronchial syndrome** associated with **deterioration of pulmonary function**, with symptoms resolving seven days after stopping use of e-cigarettes
Thota *et al.*[36] 2014	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Acute eosinophilic pneumonia**
Ring Madsen *et al.*[53] 2016	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Use of e-cigarettes with 38 mg/mL nicotine, 10 mL per week Outcome: Abdominal pain and fever, and multiple pulmonary nodules and liver lesions, lung biopsy revealed multinucleated giant cells, suggestive of a **foreign body reaction to a lipophilic material**
Carter *et al.*[54] 2017	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Current user of e-cigarettes Outcome: Sudden onset dyspnoea suspected **chemical injury**
Flower *et al.*[42] 2017	Harm	Product: E-cigarette and conventional combustible tobacco cigarette Dose taken or reported relevant behaviour: Commenced vaping 10 to 15 times per day while continuing to smoke 10 conventional combustible tobacco cigarettes per day Outcome: **Respiratory bronchiolitis-interstitial lung disease**
Miler *et al.*[56] 2017	Benefit	Product: E-cigarette Dose taken or reported relevant behaviour: A few months of e-cigarette use Outcome: **Resolution of chronic tonsillitis**
Agustin *et al.*[40] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Vaping for the past two months with overtly increased exposure time and new flavours experimentation Outcome: Dyspnoea and haemoptysis, diagnosed as **diffuse alveolar haemorrhage syndrome**
Khan *et al.*[57] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Increased use of e cigarettes during past month to help quit smoking Outcome: **Pulmonary toxicity**
Marasco *et al.*[43] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Spontaneous pneumomediastinum**
Miler and Hajek[58] 2018	Benefit	Product: Glycerol-based nicotine vaporizer (e-cigarette) Dose taken or reported relevant behaviour: A few weeks of e-cigarette use containing vegetable glycerine with low levels of nicotine (3 mg/ml) Outcome: **Resolution of chronic nasal infection**

Author(s), year	Possible benefit or harm	Case reports on respiratory diseases
Sommerfeld *et al.*[50] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Acute respiratory distress syndrome**
Viswam *et al.*[55] 2018	Harm	Product: E-cigarette (containing vegetable glycerine) Dose taken or reported relevant behaviour: Information not available Outcome: **Lipoid pneumonia**
Arter *et al.*[48] 2019	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Two months prior to presentation the patient started vaping using a Baby Smok Beast Mod device with 6% nicotine fluid five times per day for 30 minutes Outcome: **Acute eosinophilic pneumonia**
Bakre *et al.*[51] 2019	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: E-cigarettes use for three years prior to presentation Outcome: **Alveolar septal thickening** due to fibroblastic proliferation and **alveolar lining hyperplasia**
Bonilla *et al.*[44] 2019	Harm	Product: Vaping product (e-cigarette) Dose taken or reported relevant behaviour: A history of vaping just prior to both episodes of illness Outcome: Recurrent right-sided **spontaneous pneumothoraces**
Dicpinigaitis *et al.*[45] 2020	Harm	Product: Street purchased vape cartridge Dose taken or reported relevant behaviour: Symptoms presented two weeks after initiating use of a street-purchased tetrahydrocannabinol-containing vape cartridge. Outcome: **Acute respiratory failure**
Macedonia *et al.*[41] 2019	Harm	Product: E-liquid solution mixture contained vanillin, aldehydes, alcohols and other chemicals Dose taken or reported relevant behaviour: Symptoms began nine months after the subject quit smoking traditional cigarettes and transitioned solely to heavy vaping Outcome: **Bronchiolitis**
Maddock *et al.*[38] 2019	Harm	Product: E-cigarette containing nicotine and tetrahydrocannabinol Dose taken or reported relevant behaviour: Daily vaping Outcome: **Respiratory distress syndrome**
Nair *et al.*[39] 2019	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Recent commencement of vaping and frequent use of two over the counter purchased e-cigarettes liquids Outcome: **Hypersensitivity pneumonitis**
Ocampo-Gonzalez *et al.*[46] 2020	Harm	Product: E-cigarette with e-liquid containing both tetrahydrocannabinol and nicotine as well as occasional marijuana use Dose taken or reported relevant behaviour: Daily vaping with a recent change in product provider Outcome: **Interlobular septal thickening and diffuse ground glass opacities in both lungs**
Sechrist *et al.*[47] 2019	Harm	Product: E-liquid containing both tetrahydrocannabinol Dose taken or reported relevant behaviour: Vaping Outcome: **Vaping-associated lung disease**
Twohig *et al.*[52] 2019	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Use more than 10 times daily for two weeks Outcome: **Dyspnoea and cyanosis, metabolic acidosis**

4.2.1.5 Oral diseases: case reports

Four papers reported measures of oral health. Three addressed issues related to mucosal membranes or the tongue, and one related to dental caries (Table 5). The age range for three females and one male was 51–66 years. The mucosal tissue morbidities were lingua villosa nigra,[59] oral lichen planus,[60] and asymptomatic hyperpigmented tongue.[61] The identified dental-related measures were multiple smooth surface carious lesions.[62]

Table 5 Case reports on oral diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on oral diseases
Farinha *et al.*[59] 2015	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: The subject had stopped tobacco smoking and initiated electronic cigarette a few weeks before presentation Outcome: **Lingua villosa nigra** (asymptomatic black discoloration)
Bartram *et al.*[60] 2016	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Commencement of e-cigarette use Outcome: **Oral lichen planus**
Lilleker *et al.*[62] 2017	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Multiple smooth surface-active carious lesions**
St Claire *et al.*[61] 2017	Harm	Product: E-cigarette cappuccino-flavoured Dose taken or reported relevant behaviour: The patient began vaping in the week before presentation Information not available Outcome: **Asymptomatic hyperpigmented tongue**

4.2.1.6 Developmental and reproductive effects: case reports

There were no case reports on the relationship between e-cigarettes and developmental and reproductive effects.

4.2.1.7 Injuries and poisonings: case reports

There were 49 papers on injuries and poisonings. Of these, 28 were on injuries (Tables 6–10) and 21 were on poisonings (Tables 11–13).

4.2.1.7.1 Injuries

The 28 papers reporting on injuries were grouped by injury type and, where possible, by anatomical location of the sustained injuries (Tables 6–10). The causes of injury included burns (chemical and thermal) and explosions. Anatomical injury locations were further described by features such as part of the body, percentage of total skin surface area involved, thickness of the burn, presence of embedded shrapnel, and/or bone fractured. The parts of the body injured included head, face, eye, mouth (including teeth), thigh, and leg.

Eight papers were grouped under thermal burns which occurred between 2015 and 2019; they reported findings on 4 males, 2 females and 2 persons whose sex was not reported (Table 6). The age range of males was 26–35 years and for females was 30–49 years. Most burns were to the thigh and leg,[63-67] but burns to the shoulder,[68] chest,[68] and face[66 69] were also reported. The location of injury was usually indicative of whether the e-cigarette was in use or not. In general, injuries to the thigh region indicated the location of storage, whereas upper body injuries indicated that the injury occurred when the e-cigarette was in use. The percentage of total skin surface area burned ranged from 1.5% to 8%. Two papers report chemical burns, one in 2016 and one in 2018 (Table 7). Sex or age were not identified. Both injuries were the result of the inadvertent administration of e-cigarette liquid to the eye.[70 71]

Four papers reported on fractures arising from e-cigarette use between 2016 and 2019; all cases were male and were aged between 17 years and 59 years (Table 8). In most cases, the main injury was to the face and head,[72-74] for example, maxillofacial fracture, premaxilla fracture, and anterior nasal spine damage, with associated soft tissue and organ damage, as well as one spinal fracture.[75] Injuries were severe and required surgical repair and intensive care.

Eight papers were categorised as blast injuries, with injuries to the eyes,[76] nose, [77] face,[77-79] hands,[78 80-82] and chest[78] being reported (Table 9). The injuries occurred between 2016 and 2018. Most papers did not report sex or age. Again, surgical intervention was required, and two patients sustained chronic neurological damage with sensory loss and decreased motor control.

The remaining six injury papers consisted of a number of injuries arising from a combination of thermal and chemical burns and fractures which occurred between 2016 and 2018 (Table 10).[83-88] The only major difference in outcome observed from those previously reported was the reporting of a non-malignant necrotic ulcer in one case.[86] For a small number of papers, information on modification of the e-cigarette device was reported, and both no modification and modification activities were recorded. The age and sex were reported for two of the six cases; in both cases, the subjects were young males.

Table 6 Case reports on injuries and poisonings, presenting as thermal burns, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as thermal burns
Jablow *et al.*[63] 2015	Harm	Product: E-cigarette which ignited Dose taken or reported relevant behaviour: Not reported Outcome: **Partial thickness burns to patient's right leg** and circumferentially to his right knee
Goverman *et al.*[64] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Thigh burns**
Hassan *et al.*[89] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Burns**
Shastry *et al.* [68] 2016	Harm	Product: E-cigarette experimental device which exploded Dose taken or reported relevant behaviour: The patient was a paid tester for an E-cigarette company Outcome: **Burns to the shoulder and chest**
Walsh *et al.* [65] 2016	Harm	Product: E-cigarette lithium battery which self-combusted Dose taken or reported relevant behaviour: Information not available Outcome: 1.5% total body surface area mixed-depth **burn to the lateral aspect of the right thigh**
Anderson *et al.*[66] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: 2% total body surface area **burns to the face, forearm, and thigh, and bilateral corneal burns**
Serror *et al.*[67] 2017	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Not reported Outcome: **Deep thigh burns**
Benowitz *et al.*[69] 2019	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: A previous smoker who longer smoked regular cigarettes, asked her friend to bring her e-cigarette in hospital which sparked an explosion on use Outcome: Deep **first-and second-degree burns to face and hand**

Table 7 Case reports on injuries and poisonings, presenting as chemical burns, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as chemical burns
Jamison *et al.*[70] 2016	Harm	Product: E-cigarette liquid Dose taken or reported relevant behaviour: Inadvertent administration of e-cigarette liquid to the eye Outcome: **Mild ocular chemical injury**
McCague *et al.*[71] 2018	Harm	Product: E-cigarette liquid Dose taken or reported relevant behaviour: Accidental administration of e-cigarette liquid Outcome: **Ocular chemical burn**

Table 8 Case reports on injuries and poisonings, presenting as fractures with or without additional injuries, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as fractures with or without additional injuries
Archambeau *et al.*[72] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: The patient had received the device two days prior to presentation after purchasing it online and reportedly made no modifications Outcome: Complex **facial fractures and pneumocephalus**
Brooks *et al.*[73] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: Severe **damage to the anterior dentition** (fractured teeth, avulsions, and luxation) along with **fractured premaxilla and anterior nasal spine, and sustained lacerations** to the upper lip, labial mucosa, gingivae, tongue, hard palate, and facial skin
Norii *et al.*[75] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Spinal fracture**
Katz *et al.*[74] 2019	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Not reported Outcome: Comminuted and displaced **mandibular fracture with disruption of the left central and lateral incisor teeth**

Table 9 Case reports on injuries and poisonings, presenting as blast injuries to anatomical sites, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as blast injuries to anatomical sites
Bohr *et al.*[90] 2016	Harm	Product: E-cigarette battery which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Burn injury**
Khairudin *et al.*[76] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: The e-cigarette exploded a result of a modification made to the heating element of the e-cigarette device by a non-professional Outcome: **Extensive ocular injury**
Moore *et al.*[78] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Injuries and burns** to the face, left hand, and chest
Ban *et al.*[79] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Ballistic injury to the maxilla**, and associated injuries resulting in an avulsive injury
Foran *et al.*[80] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Injection injury to finger**
Satteson *et al.*[81] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Extensive thermal and blast injuries to hand**
Vaught *et al.*[77] 2017	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: Projectile **fracturing to the right naso-orbital-ethmoid complex and the anterior and posterior frontal sinus tables**, with frontal sinus outflow tract involvement
Ackley *et al.*[82] 2018	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Not reported Outcome: **Burned left thumb** with sensory loss, decreased motor control, and heavy bleeding.

Table 10 Case reports on injuries and poisonings, presenting as novel or combination injuries, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as novel or combination injuries
Cason *et al.*[83] 2016	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: **Injuries and burns** to face, left hand, and chest
Harrison *et al.*[84] 2016	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Intraoral burns, luxation injuries, and alveolar fractures**
Roger *et al.*[85] 2016	Harm	Product: E-cigarette which exploded when the patient pressed the device's button Dose taken or reported relevant behaviour: No additional relevant information reported Outcome: **Oral and abdominal burns**, oral lacerations, **tooth fracture**, and tooth avulsion
Cant *et al.*[86] 2017	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: The patient had previously been smoking 20 cigarettes a day for 30 years before starting to use electronic cigarettes to aid his smoking cessation. He reported a history of inhaling strongly on his e-cigarette and suffered extreme discomfort immediately afterwards prior to hospital presentation Outcome: **Necrotic ulcer**
Andresen *et al.*[87] 2018	Harm	Product: E-cigarette (patient fell with the device in his mouth) Dose taken or reported relevant behaviour: Information not available Outcome**: Diffuse supraglottic enema**, most severe in the epiglottis, arytenoids, and aryepiglottic folds
Chi *et al.*[88] 2018	Harm	Product: E-cigarette which exploded Dose taken or reported relevant behaviour: Information not available Outcome: Sustained **oral burns, lacerations, and tooth loss**

4.2.1.7.2 Poisonings

The 21 papers on poisonings were grouped by intent: intentional, accidental, or undeterminable (Tables 11–13). Aside from the chemical products of AB-FUBINACA, ADB-FUBINACA and acetylfentanyl, most of the papers suggested toxic nicotine levels as the principal poisoning agent. Overall, seven cases died.

The authors of six papers reported that the poisoning-related injury was intentional for the cases examined.[91-96] There was one fatality. Three suicide attempts were made by ingesting e-liquid, two injected e-liquid, and the mode of use in the sixth case was not recorded (Table 11). The cases occurred between 2013 and 2019. Sex was reported for five cases; four were male and one was female. Age was reported for 2 of the 10 cases; one of these was aged 29 years while the other was aged 51 years. A pre-diagnosis of an underlying psychiatric condition was reported in two cases, and one of these cases also reported a sexual identity disorder. Two patients self-presented at the emergency department. In one case, treatment was requested by relatives. In the remaining three cases, the nature of help sought was unknown.

Among the six cases of accidental poisonings between 2014 and 2017,[97-101] four involved children whose ages ranged from 15 months to 6 years; two of these four children died (Table 12). Sex was known for five cases; one was male and four were female. Both age and sex were not known for one case. One adult poisoning was the result of a chronic, rather than an acute, use of e-liquid. The 36-year-old adult male had been using propylene glycol with acetylfentanyl, purchased online, as a relaxation aid. Treatment with naloxone corrected his respiratory compromised condition, and he was subsequently discharged from intensive care.

In nine of the case reports, published between 2012 and 2018, the poisoning intent was not determined.[102-110] The mode of poisoning for all cases was through ingestion of e-liquid (Table 12). In one case, the patient had also consumed alcohol, and in another, the e-liquid contained a synthetic cannabinoid (AB-FUBINACA and ADB-FUBINACA). Events initiated by ingestion of the e-liquid included cardiac arrest, supraventricular tachycardia, bradycardia, and hypotension. Sex was known for five cases; all were male. Age was known for three men (24-39 years) and one child (aged 6 years). Four people died and one 6-year-old child had sensorineural hearing loss.

Table 11 Case reports on injuries and poisonings, presenting as intentional poisonings, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as intentional poisonings
Thornton *et al.*[91] 2013	Harm	Product: E-liquid injection Dose taken or reported relevant behaviour: Information not available Outcome: **Cardiopulmonary arrest**
Eberlein *et al* [92] 2014	Harm	Product: E-liquid ingestion of one capsule of nicotine containing liquid Dose taken or reported relevant behaviour: Information not available Outcome: **Intentional poisoning**
Schipper *et al.*[93] 2014	Harm	Product: E-liquid ingestion Dose taken or reported relevant behaviour: The e-liquid fillings contained a total of 420 mg of nicotine and unknown amounts of propylene glycol and glycerine Outcome: **Suicide attempt**
Chen *et al.*[94] 2015	Harm	Product: E-liquid ingestion Dose taken or reported relevant behaviour: A partially ingested bottle of whiskey, and two empty 15 mL vials of concentrated liquid nicotine (100 mg/mL) Outcome: Multiple acute infarcts, consistent with **severe anoxic brain injury resulting in death**
Martin-Kleisch *et al.*[95] 2016	Harm	Product: E-liquid ingestion Dose taken or reported relevant behaviour: 115 mL of e-liquid purchased via the Internet (propylene glycol >75%, water <3%, alcohol <2%, nicotine 19.9 mg/mL) Outcome: **Intentional poisoning**
Belkoniene *et al.*[96] 2019	Harm	Product: E-liquid intravenous injection Dose taken or reported relevant behaviour: Injection of 10 mL of e-liquid (1000 mg of nicotine diluted in propylene glycol) Outcome: **Transitory neurological impairment** with the appearance of tetraparesis, gaze palsy, and myoclonus, uncompensated lactic acidosis

Table 12 Case reports on injuries and poisonings, presenting as accidental poisonings, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as accidental poisonings
Gupta *et al.*[97] 2014	Harm	Product: Nicotine solution in refill cartridge bottle Dose taken or reported relevant behaviour: Child picked up and place refill cartridge bottle in her mouth Outcome: Potential **accidental ingestion of nicotine solution** but subsequent clinical observations were normal
Eggleston *et al.*[98] 2016	Harm	Product: E-cigarette liquid exposure Dose taken or reported relevant behaviour: No paper info not in abstract Outcome: **Paediatric death**
Gomolka *et al.*[99] 2016	Harm	Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: Accident drinking of e-liquid containing nicotine at concentration 6 mg/ml. Outcome: **Symptoms of overdose**: dizziness, flushed cheeks, dry skin, dry conjunctivae, medium-wide pupils, nervous twitching, tachycardia, and elevated blood pressure.
Rogers *et al.*[100] 2016	Harm	Product: Propylene glycol e-cigarette filled with acetylfentanyl Dose taken or reported relevant behaviour: Patient had developed the habit of using an e-cigarette with increasing frequency containing propylene glycol e-cigarette filled with acetylfentanyl in order to aid relaxation Outcome: **Respiratory depression**, pinpoint pupils, hypoxaemia, and a Glasgow Coma Scale score of 6
Seo *et al.*[101] 2016	Harm	The authors reported on a 15-month-old child fatality where the child ingested liquid nicotine, having mistaken been given it for cold medicine. Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: Accidental ingested of liquid nicotine, having mistaken it for cold medicine Outcome: Pulseless electrical activity resulting in **death**
Noble *et al.*[111] 2017	Harm	Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: 703 mg (35 mg/kg) of liquid nicotine ingested Outcome: **Severe toxicity and required intubation**

Table 13 Case reports on injuries and poisonings, presenting as poisonings with intention undetermined, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on injuries and poisonings presenting as poisonings with intention undetermined
Waldman and Sein Anand[102] 2012	Harm	Product: Nicotine from cartridges of e-cigarettes Dose taken or reported relevant behaviour: Information not available Outcome: **Cardiac arrest**
Bartschat *et al.*[103] 2015	Harm	Product: Nicotine solution vials of the brand Titanium Ice (50 mL each) Dose taken or reported relevant behaviour: Information not available Outcome: **Poisoning** (toxicological analysis revealed nicotine concentrations of 5.5 mg/mL in femoral venous blood, 136.0 mg/mL in heart blood, 12.0 mg/kg in brain tissue, 42.6 mg/kg in kidney tissue, 89.5 mg/kg in lung tissue, and a total amount of 3950 mg in the gastric contents) resulting in **death**
Garat *et al.*[104] 2016	Harm	Product: E-liquid containing propylene glycol Dose taken or reported relevant behaviour: Information not available Outcome: **Acute propylene glycol poisoning** not nicotine toxicity
You *et al.*[105] 2016	Harm	Product: Oral ingestion of e-cigarette liquid Dose taken or reported relevant behaviour: Oral injection of at least 714 mg of nicotine Outcome: **Death**
Lam *et al.*[106] 2017	Harm	Product: E-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA (synthetic cannabis). Dose taken or reported relevant behaviour: Two drops Outcome: Somnolent, confused, and agitated, with palpitation, vomiting and a short run of supraventricular tachycardia
Morley *et al.*[107] 2017	Harm	Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: Ingestion of nicotine-containing e-liquid while under the influence of alcohol Outcome: Ingested nicotine-containing e-liquid resulting in **death**
van der Meer *et al.*[108] 2017	Harm	Product: E-cigarette liquid Dose taken or reported relevant behaviour: Injection of highly concentrated liquid nicotine Outcome: **Cardiac arrest**
Demir and Topal[109] 2018	Harm	Product: E-cigarette liquid Dose taken or reported relevant behaviour: Once off drinking of e-cigarette liquid Outcome: **Bilateral sudden sensorineural hearing loss**
Paik *et al.*[110] 2018	Harm	Product: A commercial liquid nicotine bottle was found together with a cup filled with liquid suspected to be nicotine Dose taken or reported relevant behaviour: Once off oral ingestion of a high concentration of liquid nicotine Outcome: **Bradycardia and hypotension**

4.2.1.8 Exposure to e-cigarette toxins: case reports

Four papers reported on outcomes resulting from toxic exposure to the e-cigarette device or e-liquid (Table 14). Two cases involving females reported on allergic contact dermatitis,[112 113] and one case involving a female reported on facial, lip, and eyelid swelling with erythema and itching over a 6-month period.[114] The cases of allergic contact dermatitis were attributed to the material in the e-cigarette device in one instance and to the e-liquid, Cigavapor, in the other instance. The causal factor in the case of swelling with erythema and itching was unclear, but potentially included the e-cigarette device, the e-liquid, and another metal device, an eyelash curler. The fourth case involved a 13-year-old female who presented with cardiac and neurological disturbances and subsequently admitted to vaping the entire contents of an e-cigarette prior to symptom onset.[115] All cases of toxicity were resolved following medical treatment.

Table 14 Case reports on exposure to e-cigarette toxins, presenting as dermatological or poisoning symptoms, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on exposure to e-cigarette toxins presenting as dermatological or poisoning symptoms
Maridet *et al.*[112] 2015	Harm	Product: E-cigarette device Dose taken or reported relevant behaviour: Exposure to a patient's own corroded e-cigarette, corrosion deemed to be probably due to patient's hands sweat Outcome: **Allergic contact dermatitis** diagnosed following a dimethylglyoxime nickel spot test of the device
Ormerod *et al.*[114] 2017	Harm	Product: Metal e-cigarette and metal eyelash curlers used intermittently Dose taken or reported relevant behaviour: Exposure prior to symptoms unknown but following two months of product avoidance no further episodes of facial rash/swelling was noted and an improvement in the patient's hand dermatitis was observed Outcome: Facial, lip, and eyelid swelling, erythema, and itching, mild hand dermatitis. Patch testing demonstrated a **positive reaction to nickel and hydroxycitronellal and iodopropynyl butylcarbonate**
Azevedo *et al.*[113] 2019	Harm	Product: E-cigarette vaping liquid (Cigavapor which contains herbal extract, 5%, glycerine and propylene glycol) Dose taken or reported relevant behaviour: Use of e-cigarette around the time of onset of the hand dermatitis was reported Outcome: **Allergic contact dermatitis**
Hughes *et al.*[115] 2020	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Entire contents of an e-cigarette cartridge just prior to symptom onset Outcome: **Sinus tachycardia** (heart rate of 124 beats per minute) with a QRS of 86 ms and QTc of 443 ms. Urine immunoassay positive for tetrahydrocannabinol, opiates, and benzodiazepines

4.2.1.9 Other outcomes: case reports

The remaining 12 papers did not align with the adapted Academies of Sciences' umbrella terms, and are presented in Tables 15–17.

Four papers, published between 2015 and 2018, reported on the impact of changing from smoking conventional tobacco cigarettes to using e-cigarettes on therapeutic drug levels.[116-119] Patients on clozapine who switched from conventional tobacco cigarettes to e-cigarettes were reported to exhibit changes in behaviour or in clozapine levels which required adjustment to the prescribed therapeutic dosage (Table 15). Only one of the four papers reported age and sex.

Three cases reported on oxygen tissue perfusion being compromised postoperatively in e-cigarette users attending for breast surgery, including reconstruction surgery, or other post-injury skin grafting between 2016 and 2018 (Table 16).[120-122] A fourth case of oxygen depletion, due to reversible cerebral vasoconstriction, was also attributed to e-cigarette use and was reported in 2015.[123]

Two cases reported benefits attributed to e-cigarette use (Table 17). One case of decreasing severity of the symptoms of ulcerative colitis were reported.[124] The second case reporting a potential beneficial outcome of e-cigarette use was observed in a patient who switched from conventional cigarette smoking to e-cigarette vaping.[125] The previous adverse blood measures of leukocyte count and C-reactive protein normalised in the patient, who had chronic idiopathic neutrophilia. Two cases of organ donation (kidney and liver) following an intentional overdose using e-liquids with nicotine were described.[126 127]

Table 15 Case reports on other outcomes, presenting as clozapine concentrations, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on other outcomes presenting as clozapine concentrations
Berm *et al.*[116] 2015	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Switched from smoking conventional combustible tobacco cigarettes to using e-cigarettes in a subject with a suspected active psychosis Outcome: **Unexpected changes to clozapine levels**
Nonner *et al.*[117] 2016	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Switched from smoking conventional combustible tobacco cigarettes to using e-cigarettes Outcome: **Unexpected changes to clozapine levels**, resulting in a requirement to reduce the patient's clozapine dosage
Khorassani *et al.*[118] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Conversion from smoking conventional combustible tobacco cigarettes to using an e-cigarette over a 12-month period Outcome: **Unexpected changes to clozapine levels**
Kocar *et al.*[119] 2018	Harm	Product: Switch from smoking conventional combustible tobacco cigarettes to e-cigarettes Dose taken or reported relevant behaviour: Switch from smoking conventional combustible tobacco cigarettes to using an e-cigarette Outcome: **Unexpected changes to clozapine levels**

Table 16 Case reports on other outcomes, presenting as oxygen perfusion or depletion, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on other outcomes presenting as oxygen perfusion or depletion
Vannier *et al.*[123] 2015	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: Information not available Outcome: **Cerebral vasoconstriction syndrome**
Krishnan *et al.*[120] 2016	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: E-cigarette users until the date of surgery Outcome: **Drop in ViOptix tissue oximeter reading** in left breast **post-operatively** following autologous breast reconstruction
Fracol *et al.*[121] 2017	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: E-cigarette use Outcome: **Mastectomy skin flap necrosis post-operatively**, following breast reconstruction failure
Agochukwu *et al.*[122] 2018	Harm	Product: E-cigarette Dose taken or reported relevant behaviour: E-cigarette use Outcome: **Compromised perfusion to the skin flap** (autologous transfer) **post-operatively**

Table 17 Case reports on other outcomes, presenting as miscellaneous outcomes, harms or benefits

Author(s), year	Possible benefit or harm	Case reports on other outcomes presenting as beneficial outcomes
Farsalinos *et al.*[125] 2013	Benefit	Product: E-cigarette Dose taken or reported relevant behaviour: Six-month e-cigarette use following a decade of conventional tobacco cigarette use Outcome: **Reversal of chronic idiopathic neutrophilia**
Camus *et al.*[124] 2014	Benefit	Product: E-cigarette (smoking 20 cigarettes per day, converted to e-cigarette use) Dose taken or reported relevant behaviour: E-cigarette use following cessation of conventional tobacco cigarette use Outcome: **Ulcerative colitis symptoms abatement**
Rasanen *et al.*[126] 2017	Harm	Product: Subcutaneous nicotine overdose of liquid nicotine from an e-cigarette cartridge resulting in fatality in patient zero Dose taken or reported relevant behaviour: No paper info not in abstract Outcome: **Kidney donation after subcutaneous nicotine overdose to donor recipient**
Lee *et al.*[127] 2018	Harm	Product: E-cigarette cartridge Dose taken or reported relevant behaviour: 10 mL of 99% liquid nicotine (990 mg/mL) from e-cigarette cartridge Outcome: **Liver transplant after intentional nicotine ingestion to donor recipient**

4.2.2 Case series: e-cigarettes - study characterisation, harms and benefits

The authors of 37 case series reports described cases of similar, and medically interesting, morbidity or mortality outcomes that the authors attributed to e-cigarette devices or e-liquids (Tables 18–25). These case series reports quantify and characterise the aggregation of cases over a defined time period. The 37 case series papers report findings on benefits (2 papers), harms (34 papers) and possible harms (1 paper) arising from e-cigarette use or exposure. Thirty-six papers were published between 2016 and 2019, and one was published in 2011. The number of cases in the case series papers range from 2 to 371, with 15 papers reporting findings based on 2 cases and 4 papers reporting findings based on 3 cases. Six papers reported findings on between 6 and 10 cases, and eight papers reported findings on between 12 and 19 cases. The remaining four papers reported on 26, 53, 60, and 371 cases. Eight of the papers reporting on 10 or more cases were hospital chart reviews from burns centres. The earliest period covered was January 2007 to July 2016. Subsequent reports cover the period from 2012 to 2017.

The number of case series papers categorised under each of the seven umbrella headings within the adapted Academies of Sciences' framework ranged from 1 paper each under cardiovascular diseases, cancers (specifically oral carcinoma), and exposure to e-cigarette toxins (for instance, dermatitis) to 24 under injuries and poisonings, of which 19 papers were on burn and/or blast injury cases and 5 papers were on poisoning cases (mainly e-liquid intoxication). Fourteen of the poisoning cases were fatal. There were two papers under dependence and abuse liability, and both were categorised as benefits (smoking cessation). Eight case series paper were categorised under respiratory diseases. All were categorised as harms, and almost all harms were related to the lower respiratory tract (for example, acute lung injury). In total, there were six fatalities reported. No case series reports were categorised under the headings 'oral diseases' 'developmental and reproductive effects' or 'other outcomes'.

We did not present information on treatment in our mapping exercise, as we were focusing on describing the harms and benefits of e-cigarettes documented in the literature.

4.2.2.1 Dependence and abuse liability: case series

The two case series papers reporting under the heading dependence and abuse liability were from the same lead author and reported a total of five cases with a long history of conventional cigarette dependence who were able to discontinue smoking, with two cases who also eventually ceased vaping as well.[128] [129] Both papers were published in 2011 (Table 18).

Table 18 Case series papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Case series on dependence and abuse liability
Caponnetto *et al.* [128] 2011a	Benefit	Product: Three study participants with a history of combustible tobacco cigarettes use and a documented history of recurring relapses commenced using e-cigarettes to quit smoking Dose taken or reported relevant behaviour: The three participants commenced using: (1) an e-cigarette loaded with a high nicotine concentration of 7.2 mg of nicotine per cartridge two 2 years previously (2) an e-cigarette loaded with a high nicotine concentration of 7.2 mg of nicotine per cartridge 2 years previously, and (3) an e-cigarette loaded with nicotine cartridges two months previously Outcome: Each of the three study participants **discontinued combustible tobacco smoking completely**
Caponnetto *et al.* [129] 2011b	Benefit	Product: Two study participants with a history of combustible tobacco cigarettes use and suffering from depression commenced using e-cigarettes to quit smoking Dose taken or reported relevant behaviour: The participant's smoking history was and e-cigarette use commencement was: (1) 30 cigarettes per day (44 pack-years), e-cigarette loaded with a high nicotine concentration of 7.2 mg of nicotine per cartridge (2) 20–30 cigarettes per day (29 pack-years) with a significant level of nicotine dependence, e-cigarette loaded with a high nicotine concentration 7.2 mg of nicotine per cartridge Outcome: Both study participants **discontinued combustible tobacco smoking** between three and six months after commencing use of e-cigarettes

4.2.2.2 Cardiovascular diseases: case series

There was one case series paper on the relationship between e-cigarettes and cardiovascular diseases (

Table 19). The paper explored the relationships between potentially cardiotoxic volatile organic compounds in non-users of tobacco (n=87), e-cigarette users (n=17), conventional cigarette smokers (n=237), and dual users of e-cigarettes and conventional tobacco cigarettes (n=30).[130] The authors found that there were moderate differences in the raw levels of cotinine across subjects in each product category, with conventional cigarette smokers having a slightly higher cotinine level than e-cigarette users or dual users. E-cigarette users, however, had comparable mean levels of cotinine as dual users. The authors also stated that although the contribution of volatile organic compounds to tobacco-induced disease is unclear, the observation that volatile organic compound metabolites are elevated in e-cigarette users suggests that the use of these products results in volatile organic compound exposure. E-cigarette users may potentially be at a higher risk of cardiovascular injury compared to non-users.

Table 19 Case series papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case series on cardiovascular diseases
Keith *et al.* [130] 2019	Harm	Product: Non-users of tobacco (n=87), sole e-cigarette users (n=17), sole conventional combustible tobacco cigarette users (n=237), and dual users of e-cigarettes and conventional combustible tobacco cigarettes (n=30). Total population:n=371 Dose taken or reported relevant behaviour: Information on dosage or relevant behaviours was not reported. However, multivariable-adjusted models were employed to assess twenty-three urinary metabolites of tobacco-induced aldehydes and other volatile organic compounds Outcome: Sole e-cigarette users had **higher levels of cardiotoxic metabolites of acrolein, acrylamide, acrylonitrile, and xylene** compared with non-users of tobacco, but **lower levels of most volatile organic compound metabolites** compared with cigarette smokers or dual users

4.2.2.3 Cancers: case series

The case series paper reporting on cancer-related outcomes was published in 2017 and described two cases of oral carcinoma in older males (aged 59 and 66 years) with no known risk factors for oral cancer (such as family history, human papillomavirus infection, or chronic oral infections), but with a 10-year history of e-cigarette use (Table 20).[131]

Table 20 Case series papers on cancers, benefits or harms

Author(s), year	Possible benefit or harm	Case series on cancers
Nguyen *et al.* [131] 2017	Harm	Product: Two study participants with a history of e-cigarette use Dose taken or reported relevant behaviour: The participant's e-cigarette history was: (1) e-cigarettes 20 times per day for the past 13 years, and (2) 30 e-cigarettes per day for the past 13 years Outcome: (1) Histopathology revealed a moderately collagenous connective tissue stroma infiltrated with nests and islands arising from e-cigarette use (2) a diagnosis of **basaloid squamous cell carcinoma** was made.

4.2.2.4 Respiratory diseases: case series

The eight paper on respiratory diseases reported findings of between 2 and 60 cases each and were published in 2019 (Table 21). The first paper reported on 60 young adult patients (48 males and 12 females) with lung injury associated with e-cigarettes or vaping, who were seen in Intermountain Healthcare (13 hospitals or outpatient clinics), Utah.[132] More than half were admitted to intensive care, and two died. Many of the 58 survivors had residual abnormalities at short-term follow-up. The second paper reported on two adolescents, one male and one female, with a history of asthma who experienced respiratory failure.[133] The third paper reported on six males presenting with a variety of respiratory and gastrointestinal symptoms who had computer tomography scans of the chest which revealed multilobar ground glass opacities with subpleural sparing in the lungs.[134] All six reported regular use of vaporised cannabis and nicotine products. The patients were treated, and no fatalities occurred. The seventh paper in Table 21 reported on eight American males with a history of e-cigarette use who presented with common features of serious lung damage; seven recovered and one died.[135] The authors concluded that the respiratory tract damage arose from their vaping practices. The remaining four papers described other respiratory-related damage.[136-138] [139] These four papers reported on observed pathologies in 12–53 cases. These included, but were not limited to, hypoxaemic respiratory failure, acute lung injury, diffuse alveolar damage, and/or pneumonia. The histological findings were not specific, but foamy macrophages and pneumocyte vacuolisation were seen in all cases. Other histological findings included patterns of giant cell interstitial pneumonia,

hypersensitivity pneumonitis, and diffuse alveolar haemorrhage. There were three fatalities reported in these four papers; the other patients recovered, but only after hospitalisation.

Table 21 Case series papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case series on respiratory diseases
Blagev *et al.*[132] 2019	Harm	Product: Sixty patients using e-cigarettes or vaping Dose taken or reported relevant behaviour: Use of e-cigarettes Outcome: **Severe lung injury** with constitutional and gastrointestinal symptoms at short-term follow-up, many patients had residual abnormalities
Bradford *et al.*[133] 2019	Harm	Product: Two study participants with a history of recent and past e-cigarette use and asthma Dose taken or reported relevant behaviour: The was limited recorded history on the participant's e-cigarette history: for participant (1) a significant personal history of e-cigarette use but specific sue was not specified, (2) a history of e-cigarette use, the extent of which was not documented and secondary exposure to cigarette smoke at home. Outcome: **Hypercarbic respiratory failure** secondary to status asthmaticus requiring veno-venous extracorporeal membrane oxygenation, with slow recovery on extensive bronchodilator and steroid regimens, in both patients
Butt *et al.*[134] 2019	Harm	Product: Seventeen patients using e-cigarettes or vaping Dose taken or reported relevant behaviour: Use of e-cigarettes Outcome: **Acute lung injury**
Henry *et al.*[136] 2019	Harm	Product: Nineteen patients using e-cigarettes or vaping Dose taken or reported relevant behaviour: Use of e-cigarettes Outcome: **Acute eosinophilic pneumonia**, diffuse alveolar damage, organising pneumonia, and lipoid pneumonia
Kalininskiy *et al.*[137] 2019	Harm	Product: Twelve patients using e-cigarettes or vaping Dose taken or reported relevant behaviour: Use of e-cigarette containing tetrahydrocannabinol oil Outcome: Admission to the intensive care unit for **hypoxaemic respiratory failure,** no deaths occurred
Layden *et al.*[138] 2020	Harm	Product: Fifty-three persons using e-cigarettes Dose taken or reported relevant behaviour: Not reported Outcome: **Respiratory symptoms (bilateral infiltrates), gastrointestinal symptoms** and constitutional symptoms requiring hospitalisation, one third required intubation and mechanical ventilation; **one death** was reported
Mukhopadhyay *et al.*[135] 2020	Harm	Product: Eight persons using e-cigarettes Dose taken or reported relevant behaviour: Not reported Outcome: Diffuse bilateral ground glass opacities, **acute lung injury**, including organising pneumonia and/or diffuse alveolar damage
Triantafyllou *et al.*[139] 2019	Harm	Product: Six persons using e-cigarettes Dose taken or reported relevant behaviour: Use of vaporised cannabis and nicotine product Outcome: **Bilateral, multifocal alveolar opacifications** on chest x-ray. No fatalities occurred.

4.2.2.5 Oral diseases: case series

There were no case series papers on the relationship between e-cigarettes and oral diseases.

4.2.2.6 Developmental and reproductive effects: case series

There were no case series papers on the relationship between e-cigarettes and developmental or reproductive effects.

4.2.2.7 Injuries and poisonings: case series

Twenty-four papers reported on injuries and poisonings arising from e-cigarette use and exposure; of these papers, 19 reported on injuries (Table 22). and 5 reported on poisonings (Tables 23 and 24).

4.2.2.7.1 Injuries

The 19 case series papers on injuries were published between 2016 and 2019 (Table 22). Of the 19 case series papers which reported on burns and blast injuries, 10 reported two or three cases each and 9 reported on 8 to 14 cases. Burns were categorised by body location, the percentage of total body surface area covered, and the nature of the accident. Injuries were reported on the lower body (thigh, buttock, leg hand, scrotum, penis, and calf), upper body (finger, hand, wrist, forearm, upper arm, and ipsilateral fingers), and face (face, bilateral corneal burns and decreased visual acuity, and a unilateral corneoscleral laceration with prolapsed iris tissue and hyphaemia). The greatest proportion of injuries were to the thigh[67 140-150 151] and hand.[67 140 142 143 146 148-150 152-154] Burns ranged from 1% to 16% of total body surface area and ranged from minor superficial burns to deep tissue injury that necessitated autologous split-thickness skin grafts. One case series reported that 8 of 14 patients required skin grafting.

Four different mechanisms of burns were described: thermal burns with flames due to the phenomenon of 'thermal runaway', chemical alkali burns caused by spreading of the electrolyte solution, thermal burns without flames due to overheating, and blast lesions following explosion. [67 146]

E-cigarette explosions or blasts were explicitly reported in 12 papers..[67 140-143 146 148 151-156] As well as burns, some cases also experienced other injuries. These included injury to the maxilla, resulting in bone and anterior maxillary tooth loss requiring reconstruction, while another patient experienced a severe blast injury to the mouth and hand, which ultimately resulted in loss of a digit and extensive injury to the soft palate and front teeth.

No fatalities were reported. Some patients achieved full recovery, although a number of patients had a lifetime disability that required ongoing medical attention.

Table 22 Case series papers on injuries and poisonings, presenting as burns and blast injuries, benefits or harms

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings, presenting as burns and blast injuries
Brownson *et al.* [140] 2016	Harm	Product: E-cigarette the lithium-ion battery explosions Dose taken or reported relevant behaviour: Not reported Outcome: Patients experienced **flame burns, chemical burns, and blast injuries,** to the face, hands, and thigh or groin injuries with substantial implications for cosmetic and functional outcomes in the 15 people reported on. **Tooth loss, traumatic tattooing, and extensive loss of soft tissue**, requiring operative debridement and closure of tissue defects also occurred
Herlin *et al.* [141] 2016	Harm	Product: E-cigarette battery explosion Dose taken or reported relevant behaviour: Not reported Outcome: Two study participants experienced: (1) 5% total body surface area **burn lesion on his right thigh** followed by a well-conducted excision, however he had an incomplete skin graft take and persistent severe pain, suggesting a partial elimination of chemical agents during excision (2) 3% total body surface area burn on the **inner side of his thigh** requiring excision and a split-thickness skin graft on the burn area
Kite *et al.* [152] 2016	Harm	Product: E-cigarettes devices explosion Dose taken or reported relevant behaviour: Use of homemade vaporizer, and commercially purchased mechanical vaporizer Outcome: Two study participants experienced: (1) a **combustion injury to the maxilla**, resulting in bone and anterior maxillary tooth loss requiring

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings, presenting as burns and blast injuries
		reconstruction, and (2) a severe **blast injury to the hand**, which ultimately resulted in loss of a digit
Kumetz *et al.* [142] 2016	Harm	Product: E-cigarette device which exploded or ignited spontaneously Dose taken or reported relevant behaviour: Patients experienced adverse events from: (1) e-cigarette device exploded in the patient's mouth, (2) the spontaneous ignition of an e-cigarette in the patient's pocket Outcome: Two study participants experienced injury: (1) **facial injuries and burns** sustained following presentation, the patient was fitted for a maxillary prosthetic retainer and underwent several dental implant surgeries, and (2) **thermal injuries to the right hand** and full-thickness **injury to the patent's thigh**
Nicoll *et al.* [143] 2016	Harm	Product: E-cigarette device in which the single-cell rechargeable lithium-ion exploded Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of a single-cell rechargeable lithium-ion Outcome: Two study participants experienced burns: (1) 4% total body surface area superficial **partial-thickness burns** in addition to minor superficial right hand burns which was debrided and grafted (2) 3% total body surface area **superficial partial-thickness burns to thigh and right hand** minor superficial burns excised under general anaesthetic
Sheckter *et al.* [144] 2016	Harm	Product: E-cigarette device which spontaneous combustion Dose taken or reported relevant behaviour: Patients experienced adverse events from the spontaneous explosion of an e-cigarette device Outcome: Three study participants experienced burns: (1) a 15% total body surface area circumferential deep partial-thickness and full-thickness leg burn (2) a 7% total body surface area non-circumferential **mixed partial-thickness and full-thickness burn to the lateral thigh and calf**, and (3) a 2% total body surface area **burn to his right lateral thigh**, all patients recovered
Arnaout *et al.* [145] 2017	Harm	Product: E-cigarette-related burns Dose taken or reported relevant behaviour: Patients experienced adverse events from the spontaneous explosion or ignition of an e-cigarette device Outcome: Twelve study participants experienced burns with a mean total body surface area of **burns** sustained was 2.5% of mixed depth. The most common anatomical area burned was the **thigh** (83%; n=10) with a mean duration of 23.1 days (±5 days) to heal with conservative management
Jiwani *et al.* [146] 2017	Harm	Product: E-cigarette-related thermally injured Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of e-cigarette devices Outcome: Ten study participants experienced **burns** located on the **thigh** (80%) and the **hand** (50%), with a mean of 3% of total body surface area affected by thermal burns with flames, blast lesions, chemical alkali burns and thermal burns without flames
Paley *et al.*[155] 2017	Harm	Product: E-cigarette-related explosion Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of e-cigarette devices Outcome: Two study participants experienced (1) **bilateral corneal burns** and decreased visual acuity, and (2) bilateral corneal burns, decreased visual acuity and unilateral corneoscleral laceration with prolapsed iris tissue and hyphaemia.
Patterson *et al.* [147] 2017	Harm	Product: E-cigarette-related ignition and explosion Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of e-cigarette devices

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings, presenting as burns and blast injuries
		Outcome: Two study participants experienced (1) **injury to thigh and penis**, and (2) **facial burn and corneal abrasions**
Ramirez *et al.*[148] 2017	Harm	Product: E-cigarette-related burns Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of e-cigarette devices Outcome: Thirty study participants experienced adverse events arising from mainly explosions (identified as the inciting event in 26 of the 30 injuries (87%) requiring hospital admission and nine requiring surgery) with 4% of total body surface area **burns**. The **thighs, hands, and genitalia** were the most common sites of injury
Serror *et al.*[157] 2017	Harm	Product: E-cigarettes related explosions Dose taken or reported relevant behaviour: Patients experienced adverse events from the explosion of e-cigarette devices Outcome: Ten study participants experienced **burns mainly to the thigh (80%) and the hand (50%)** with a mean coverage of 3% of total body surface area due to thermal burns with flames, blast lesions, chemical alkali burns caused by spreading of the electrolyte solution and thermal burns without flames due to overheating
Smith *et al.* [149] 2017	Harm	Product: E-cigarettes related explosions Dose taken or reported relevant behaviour: Patients experienced adverse events from the burns caused by e-cigarette device's exploding Outcome: Two hundred and nineteen study participants experienced adverse events arising from **burns mainly located at the face, fingers, hands, wrists, forearms, upper arms, thighs, knees, lower legs, feet, and buttocks**. Significant morbidity was reported, with pain both from the burn injury itself and because of surgical treatment. Additional lifelong morbidity resulted from permanent scar formation was also noted
Treitl *et al.*[158] 2017	Harm	Product: E-cigarettes related spontaneous combustion of lithium-ion batteries Dose taken or reported relevant behaviour: Patients experienced adverse events from the **burns** caused by e-cigarette device's exploding Outcome: Three study participants experienced **adverse events arising from spontaneous combustion**. All were treated with debridement and local wound care and fully recovered without sequelae.
Harshman *et al.* [150] 2018	Harm	Product: E-cigarettes related spontaneous combustion of device Dose taken or reported relevant behaviour: Patients experienced adverse events from burns caused by e-cigarette device's exploding Outcome: Two study participants experienced **adverse events from burns** had: (1) mixed partial-thickness and full-thickness flame burns to right anterolateral thigh, buttock, and leg, and inner thigh, burns were debrided and successfully covered with autologous split-thickness skin grafts, and (2) deep partial-thickness and full-thickness burns to right anteromedial thigh and superficial partial-thickness burns to his right hand, covering 3% total body surface area burns were debrided
Hickey *et al.* [153] 2018	Harm	Product: E-cigarettes related spontaneous combustion of device Dose taken or reported relevant behaviour: Patients experienced adverse events from the burns caused by e-cigarette device's exploding Outcome: Fourteen study participants experienced the adverse events of **second- and third-degree burns** followed by deep and superficial second-degree burns. The average total body surface area affected was 4.7%. Isolated lower extremity burns, and lower extremity and hand burns occurred. Nine patients required surgery under general anaesthesia, eight required skin grafting. The mean hospital length of stay was 6.6 days

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings, presenting as burns and blast injuries
Maraqa *et al.* [154] 2018	Harm	Product: E-cigarette explosion predominantly attributed to its lithium-ion battery Dose taken or reported relevant behaviour: Patients experienced adverse events from the burns caused by e-cigarette device's exploding Outcome: Eight study participants experienced **adverse events arising from, mainly, explosions** resulting in partial- and full-thickness **burns**, 4% to 16% total body surface area to lower extremities, hand, scrotum/penis and chest. Two patients (29%) required skin grafting
Gibson *et al.* [151]. 2019	Harm	Product: E-cigarette burns from e-cigarette device or from batteries Dose taken or reported relevant behaviour: Not reported Outcome: Fourteen participants experienced adverse events arising mainly from **burns**. Burn size ranged from <1% to 6% total body surface area, majority to thighs with partial- or full-thickness burns. Three patients required excision and autografting; all three had suffered full-thickness burns. The average time to recovery was 24.5 days
Simpson *et al.* [156] 2019	Harm	Product: e-cigarette-related injuries arising from blast injuries from explosion of the device, chemical injuries from leakage of battery fluid, and flame injuries from ignition of the lighter's contents Dose taken or reported relevant behaviour: Patients experienced adverse events from e-cigarette device's malfunction Outcome: Twelve study participants experienced **blast injuries** from explosion of the device, chemical injuries from leakage of battery fluid, and flame injuries from ignition of the lighter's contents

4.2.2.7.2 Poisonings

Five case series papers on poisonings were published between 2016 and 2019 (Tables 23 and 24). Three papers reported intentional nicotine poisoning in six cases (three papers each reported on two cases), one of which resulted in death.[159-161] One paper reported on two fatalities arising from the use of a new fentanyl derivative, 4-fluorobutyrfentanyl, vaped via an e-cigarette.[162] The fifth paper was a retrospective evaluation of the scientific literature on cases of e-liquid nicotine intoxication. The authors identified 26 case reports or case series describing a total of 31 patients who suffered from e-liquid intoxication.[163] All intoxications in patients up to the age of 6 years were reported as unintentional, whereas nearly all cases of patients between the ages of 13 and 53 years were due to suicide attempts. Eleven of the 31 patients captured in the retrospective evaluation died. Three of the more prevalent symptoms of e-liquid intoxication were tachycardia, altered mental status, and vomiting. The paper concluded that the role of propylene glycol and vegetable glycerine in e-liquid intoxications was unclear, but suggested that the similarity between nicotine and propylene glycol toxicity symptoms led the authors to believe that a cumulative effect cannot be excluded.

Table 23 Case series papers on injuries and poisonings, presenting as intentional poisonings, benefits or harms

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings presenting as intentional poisonings
Jalkanen *et al.* [159] 2016	Harm	Product: E-cigarette liquid containing nicotine Dose taken or reported relevant behaviour: Patients attempted suicide using (1) 100 mg/mL) liquid nicotine (2) taking alcohol and 75 mg of diazepam and 10 mL of nicotine-containing fluid injected subcutaneously Outcome: Two study participants **attempted suicide** with the following outcomes (1) metabolic acidosis, treatment in intensive care and fully **recovery**, and (2) loss of consciousness, treatment in emergency medical care and subsequent **death**
Sommerfeld *et al.* [160] 2016	Harm	Product: E-liquid containing nicotine use for suicide attempts by oral and intravenous poisoning Dose taken or reported relevant behaviour: Patients attempted suicide via (1) oral poisonings with a nicotine concentration at admission of 0.8mg/L, and (2) intravenous poisonings with a cotinine concentration at admission of 1.3 mg/L Outcome: Two study participants **attempted suicide** with the following outcomes (1) acute nicotine poisoning without convulsions, and (2) unconsciousness and slow respiration
Rojkiewicz *et al.* [162] 2017	Harm	Product: E-liquid containing fentanyl derivative, 4-fluorobutyrfentanyl Dose taken or reported relevant behaviour: Two cases of intoxication with a (1) 91 ng/mL blood concentration of 4-fluorobutyrfentanyl, and (2) blood concentration 112 ng/mL of 4-fluorobutyrfentanyl Outcome: **Death in both cases**
Park *et al.* [161] 2018	Harm	Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: Patients attempted suicide via oral poisonings presenting with levels of (1) 23 mg/kg of nicotine, and (2) 30 mg/kg of nicotine Outcome: Two study participants presented with (1) metabolic acidosis leading to **cardiac arrest**, and (2) transient cardiomyopathy leading to cardiac arrest. Both patients **survived**

Table 24 Case series papers on injuries and poisonings, presenting as accidental poisonings, benefits or harms

Author(s), year	Possible benefit or harm	Case series on injuries and poisonings presenting as accidental poisonings
Maessen *et al.*[163] 2019	Harm	Product: E-liquid containing nicotine Dose taken or reported relevant behaviour: In the survivors, the highest plasma concentration of nicotine was 800 µg/L-1, while the lowest concentration in the non-survivors was 1600 µg/L-1 Outcome: Thirty-one patients presented with **unintentional or intentional intoxications following e-liquid containing nicotine ingestion**. Intoxications under the age of 6 years were unintentional, whereas nearly all cases between the ages of 13 and 53 years were suicide attempts. The three most prevalent symptoms of e-liquid intoxication were **tachycardia, altered mental status, and vomiting**. **Eleven** cases resulted in the **death** of the patient

4.2.2.8 Exposure to e-cigarette toxins: case series

One paper reported on two cases of contact dermatitis caused by nickel release from e-cigarettes in 2018 (Table 25). The first case was a 50-year-old man and the second was a 38-year-old care assistant.[164] Symptoms in both patients receded on following medical advice to stop vaping.

Table 25 Case series papers on exposure to e-cigarette toxins, presenting as dermatological symptoms, benefits or harms

Author(s), year	Possible benefit or harm	Case series on exposure to e-cigarette toxins presenting as dermatological symptoms
Shim *et al.* [164] 2018	Harm	Product: E-cigarettes device material: nickel release Dose taken or reported relevant behaviour: Two patients presented with adverse skin condition cause by materials in the composition of e-cigarette device, the conditions were (1) intermittent facial and hand dermatitis, and (2) pruritic patches on palmar surface of right hand Outcome: Two study participants experienced adverse events of **contact dermatitis**. Symptoms in both patients receded on following medical advice to stop vaping

4.2.2.9 Other outcomes: case series

There were no case series papers on the relationship between e-cigarettes and other outcomes.

4.2.3 Information or surveillance system reports: e-cigarettes

4.2.3.1 Study characterisation: e-cigarettes

There were 34 papers reporting data on e-cigarette and e-liquid-related harms from information or surveillance systems (Tables 26–31). Surveillance systems are the systematic and continuous collection, analysis, and interpretation of data, which are closely integrated with the timely and coherent dissemination of the results so that action can be taken.[27]

Reports from surveillance systems provided statistical quantification of the geographic distribution and temporal trends in e-cigarette-related adverse outcomes. The 34surveillance papers reporting on harms or possible harms related to e-cigarettes were published between 2013 and 2019. The surveillance papers were based on reports from Canada, Spain, the UK, the USA, and one survey included populations from 10 countries across Europe. The majority of surveillance papers (27 out of 34) were on injuries and poisonings, while the other category of note was respiratory diseases (4 papers out of 34). The number of surveillance papers categorised under the adapted Academies of Sciences' framework were: 1 on dependence and abuse liability; 4 on respiratory diseases (mainly lung injury); 1 on developmental and reproductive effects; 27 on injuries and poisonings, of which 4 describe injuries (mainly thermal burns) and 23 describe poisonings (mainly nicotine); and 1 on exposure to e-cigarette toxins. No surveillance papers were categorised under the headings 'cardiovascular diseases', 'cancers', 'oral diseases' or 'other outcomes'.

4.2.3.2 Harms: e-cigarettes

A selection of recent harms identified through surveillance systems reports are as follows:

- As of 20 September 2019, investigators identified a total of 908 cases of vaping-related pulmonary disease across 45 states in the USA and the U.S. Virgin Islands; of these, 495 were confirmed cases and 413 were suspected cases.[165]
- As of 15 October 2019, 86% of 867 patients in the USA with lung injury associated with use of e-cigarettes or other vaping products reported using tetrahydrocannabinol-containing products in the 3 months preceding symptom onset.[166]
- There was an estimated annual national incidence of 835 injuries in the USA related to e-cigarettes between 2008 and 2017; these injuries were mainly thermal burns.[167]
- In 2018, the annual number of e-cigarette poisoning cases increased to 2,901 in the USA.[168] Approximately two-thirds (64.8%) of all poisonings occurred in children aged under 5 years, and 14.7% were children aged 5–17 years or young adults aged 18–24 years. A small proportion of cases, equating to two or three cases each year since 2013, developed life-threatening symptoms, and cases with more serious medical outcomes tended to be exposed to a higher quantity of e-liquid or nicotine. The same trends over time, and pattern of poisonings occurring in children, were identified in Canada and the UK.
- A surveillance paper on the toxicology of e-cigarette constituents reported adverse events affecting the respiratory system, the cardiac system, and the immune system, as well as chemical burns.[169]

4.2.3.2.1 Dependence and abuse liability: surveillance papers

The 2013 surveillance paper reported under the heading of dependence and abuse liability was based on findings from state tobacco quit lines in the USA (Table 26). Both e-cigarette user groups (those who had tried e-cigarettes for 1 month or more, and those who had used e-cigarettes for less than 1 month) were significantly less likely to be tobacco abstinent at the end of a 7-month survey period compared with participants who had never tried e-cigarettes. [170]

Table 26 Surveillance papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on dependence and abuse liability
Vickerman *et al.*[170] 2013	Harm	The authors investigated the prevalence of e-cigarette use among tobacco users who sought help from state tobacco quit lines, the reasons for their use, and whether e-cigarettes impact a **user's ability to successfully quit tobacco,** and described the differences between state quit line callers who had used e-cigarettes for 1 month or more, had used e-cigarettes for less than 1 month, or had never tried e-cigarettes. Nearly one-third (30.9%) of respondents reported ever using or trying e-cigarettes; most of those had used e-cigarettes for a short period of time (61.7% for less than 1 month). The most frequently reported reasons for use were to help quit other tobacco (51.3%) or to replace other tobacco (15.2%). Both e-cigarette user groups were significantly less likely to be tobacco abstinent at the time of the 7-month survey compared with participants who had never tried e-cigarettes (30-day point prevalence quit rates: 21.7% and 16.6% versus 31.3%, $p<0.001$).

4.2.3.2.2 Cardiovascular diseases: surveillance papers

There were no surveillance papers on the relationship between e-cigarettes and cardiovascular diseases.

4.2.3.2.3 Cancers: surveillance papers

There were no surveillance papers on the relationship between e-cigarettes and cancers.

4.2.3.2.4 Respiratory diseases: surveillance papers

Four papers reported on respiratory outcomes in e-cigarette users (Table 27). All papers reported on populations in the USA and were published in 2019.

The first surveillance paper investigated the national outbreak of lung injury associated with e-cigarette or other vaping product use in the USA.[166] Based on data collected by 15 October 2019, 86% of 867 patients with lung injury associated with the use of e-cigarettes or other vaping products reported using tetrahydrocannabinol-containing products in the 3 months preceding symptom onset. Analyses of tetrahydrocannabinol-containing products identified potentially harmful constituents, such as vitamin E acetate and medium-chain triglyceride oil.

The second surveillance paper reported on more than 200 probable cases of acute lung injury, potentially associated with vaping, in 25 states.[171] Five adults aged 18–35 years (out of the more than 200 probable cases) were diagnosed with acute lung injury potentially associated with e-cigarette use. Patients experienced several days of worsening dyspnoea, nausea, vomiting, abdominal discomfort, and fever. All patients demonstrated tachypnoea, hypoxaemia, and bilateral lung infiltrates on chest X-ray. All shared a history of recent use of marijuana oils or concentrates in e-cigarettes. All of the products used were electronic vaping pens/e-cigarettes that had refillable chambers or interchangeable cartridges with tetrahydrocannabinol vaping concentrates or oils, all of which were purchased on the street. Three patients also used nicotine-containing e-cigarettes, and two of the patients smoked marijuana or conventional tobacco cigarettes. No other illicit drugs were used by the patients. All patients were hospitalised for hypoxaemic respiratory failure. All patients survived following intensive treatment.

The third surveillance paper reported on a vaping-related pulmonary disease outbreak in the USA and covered the period from July to September 2019.[165] Using an online mining tool, a total of 119 confirmed and suspected cases were detected in 16 states by 28 August 2019. The number of cases more than doubled by 6 September 2019, reaching a total of 288 cases across 28 states. As of 20 September 2019, investigators identified a total of 908 cases of vaping-related pulmonary disease across 45 states in the USA and the U.S. Virgin Islands, of which 495 were confirmed cases and 413 were suspected cases.

The final surveillance paper described the characteristics of medical care, potentially related conditions, and exposures among 83 patients in Utah.[172] Of the total study population, 70 (89%) were hospitalised, 39 (49%) required breathing assistance, and many reported pre-existing respiratory and mental health conditions. Among 53 interviewed patients, all of whom reported using e-cigarette (or vaping) products within 3 months of the onset of an acute lung injury, 49 (92%) reported using products containing tetrahydrocannabinol (without nicotine), 35 (66%) reported using nicotine-containing products (without tetrahydrocannabinol), and 32 (60%) reported using both tetrahydrocannabinol- and nicotine-containing products.

Table 27 Surveillance papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on respiratory diseases
Blount *et al.*[166] 2019	Harm	The authors investigated a national outbreak of **lung injury associated with e-cigarette, or vaping, product use**. Based on data collected as of 15 October 2019, 86% of 867 e-cigarette, or vaping, product use-associated lung injury patients reported using tetrahydrocannabinol-containing products in the 3 months preceding symptom onset. Analyses of tetrahydrocannabinol-containing product samples by Food and Drug Administration and state public health laboratories have identified potentially harmful constituents in these products, such as vitamin E acetate, medium-chain triglyceride oil, and other products. Vitamin E acetate, in particular, might be used as an additive in the production of e-cigarette, or vaping, products; it can also be used as a thickening agent in tetrahydrocannabinol products. Inhalation of vitamin E acetate might impair lung function.

Author(s), year	Possible benefit or harm	Surveillance papers on respiratory diseases
Davidson *et al.*[171] 2019	Harm	The authors reported on more than 200 possible cases of **acute lung injury potentially associated with vaping** reported from 25 states. During July and August 2019, five patients were identified at two hospitals in North Carolina with acute lung injury potentially associated with e-cigarette use. The patients were adults aged 18–35 years, and all experienced several days of worsening dyspnoea, nausea, vomiting, abdominal discomfort, and fever. All patients demonstrated tachypnoea with increased difficulty with breathing on examination, hypoxaemia (pulse oximetry <90% on room air), and bilateral lung infiltrates on chest X-ray. All five patients shared a history of recent use of marijuana oils or concentrates in e-cigarettes. All of the products used were electronic vaping pens/e-cigarettes that had refillable chambers or interchangeable cartridges with tetrahydrocannabinol vaping concentrates or oils, which were all purchased on the street. Three of the patients also used nicotine-containing e-cigarettes, and two of the patients smoked marijuana or conventional combustible tobacco cigarettes, although none used other illicit drugs. All five patients were hospitalised for hypoxaemic respiratory failure. All of the patients survived.
Hswen *et al.*[165] 2019	Harm	The authors reported, using real-time digital surveillance techniques, an integrated view of the **vaping-related pulmonary disease** outbreak in the USA since late July 2019. The authors collected online information from disparate sources including news aggregators, eyewitness reports, and validated official alerts. The authors curated and classified the data by disease case, location, and time. The first 8 suspected cases were detected by the authors' online mining tool on 25 July 2019 in Wisconsin. By 28 August, a total of 119 confirmed and suspected cases had been detected in 16 states. The number of cases more than doubled by 6 September 2019, reaching a total of 288 cases across 28 states. By 11 September, the number of cases had increased to 522, spanning 39 states and the U.S. Virgin Islands. As of 20 September 2019, the authors identified a total of 908 cases of vaping-associated severe pulmonary disease across 45 states in the USA and the U.S. Virgin Islands: 495 confirmed cases and 413 suspected cases. A total of 8 deaths were identified in California, Kansas, Illinois, Indiana, Minnesota, Oregon, and Missouri. The authors concluded that their findings highlighted the emerging epidemic.
Lewis *et al.*[172] 2019	Harm	The authors described the characteristics of medical care, potentially related conditions, and exposures among 83 patients in Utah, and detailed medical abstractions were completed for 79 patients (95%). Of the 79 patients, 70 (89%) were hospitalised, 39 (49%) required breathing assistance, and many reported pre-existing respiratory and mental health conditions. Among 53 interviewed patients, all of whom reported using e-cigarette, or vaping, products within 3 months of the **acute lung injury**, 49 (92%) reported using any products containing tetrahydrocannabinol, 35 (66%) reported using any nicotine-containing products, and 32 (60%) reported using both. Product sample testing at the Utah Public Health Laboratory showed evidence of vitamin E acetate in 17 of 20 (89%) tetrahydrocannabinol-containing cartridges, which were provided by 6 of the 53 interviewed patients.

4.2.3.2.5 Oral diseases: surveillance papers

There were no surveillance papers on the relationship between e-cigarettes and oral diseases.

4.2.3.2.6 Developmental and reproductive effects: surveillance papers

Trends in e-cigarette use among pregnant women in the USA were reported in one surveillance paper and indicate that 7% of women with a live birth in Oklahoma and Texas reported using e-cigarettes shortly before, during, or after pregnancy (Table 28).[173] Of note, 1.4% reported using e-cigarettes during pregnancy.

Table 28 Surveillance papers on developmental and reproductive effects, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on developmental and reproductive effects
Kapaya *et al.* [173] 2019	Potential harm	The authors reported on the use of electronic vaping products in women around the time of pregnancy in 2015. The authors found that 7% of women with a recent live birth in Oklahoma and Texas reported **using electronic vaping products shortly before, during, or after pregnancy**, with 1.4% reporting use during pregnancy. Among prenatal electronic vaping product users, 38.4% reported using products containing nicotine, and 26.4% did not know if the products they used contained nicotine.

4.2.3.2.7 Injuries and poisonings: surveillance papers

Twenty-seven surveillance papers reported findings on injuries and poisonings arising from e-cigarette use and exposure. Four papers reported on burns (Table 29) and 23 papers reported on poisonings (Table 30).

4.2.3.2.7.1 Injuries

All papers publishing surveillance data on burn-related injuries were from the USA and were prepared using information from six federal agencies: the United States Department of Health and Human Services; the Food and Drug Administration; the Federal Aviation Administration; the United States Consumer Product Safety Commission, including the National Electronic Injury Surveillance System; the United States Coast Guard; and the United States Fire Administration (Table 29). Concerns within federal agencies regarding e-cigarette-related burn injuries arose following alarms raised by a range of individuals and regulatory bodies. Information from professionals on the ground, in the media, in the scientific literature, and in reports raised awareness of a new fire risk leading to possible adverse events; for example, a report on fire risk arising from e-cigarettes in flight baggage and e-cigarette-related burns presenting for hospital admissions.

A number of reports from USA hospital emergency departments have identified e-cigarettes as a new mechanical and chemical risk to health. Using actual case reports from emergency departments, it has been estimated that the USA national average of e-cigarette injury between 2008 and 2017 was 835 per year.[167]

Most of the injuries were thermal burns.[167 174 175] The primary location of injury was in the lower extremity,[167 174] followed by the upper extremity, including hands.[167] The authors determined that the findings demonstrated a significant increase in the number of e-cigarette-related injuries over the total study period (2008–2017),[167 175 176] particularly in males under the age of 45 years.[167]

Table 29 Surveillance papers on injuries and poisonings, presenting as burns and/or blast injuries, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as burns and/or blast injuries
Corey *et al.* [174] 2016	Harm	The authors reported findings from 2016 United States National Electronic Injury Surveillance System data. In that year, 26 **ENDS battery-related burn cases** were reported, which translates to a national estimate of 1,007 (95% CI: 357–1,657) injuries presenting in the USA due to ENDS. The burns were mainly thermal in nature (80.4%) and mainly affected the upper leg/lower trunk (77.3%). Examination of the case narrative field indicated that at least 20 of the burn injuries occurred while ENDS batteries were in the user's pocket.
Rudy *et al.* [175] 2016	Harm	The authors reported on electronic nicotine delivery system (ENDS)-associated overheating, fire, or explosion events since 2009. Using data from 4 USA federal agencies, scientific literature, and media outlets, the authors identified 92 **overheating, fire, or explosion events** in the USA, of which 45 (49%) injured 47 people, and 67 (73%) involved property damage beyond the product. Events were identified in media outlets (n=50; 54%) and reported to 4 agencies (n=42; 46%). The report rate peaked at an average of 6 reports per month in late 2013 with a smaller peak of 3–4 reports per month in the second quarter of 2015. All reports were incomplete, and events exhibited variability. The authors suggested that more comprehensive reporting could assist future analyses and may help to identify root causes and contributors to the overheating, fire, or explosion events.
Rossheim *et al.* [176] 2018	Harm	The authors used current surveillance data to estimate the actual occurrence of cases of **explosions and burn injuries** on the basis that the recorded incidence is likely to underestimate actual occurrences. Sampling weights were applied in order to make conservative national incidence estimates. The authors concluded that, from 2015 to 2017, there were an estimated 2,035 e-cigarette explosion and burn injuries presenting to USA hospital emergency departments (95% CI: 1,107–2,964). The authors concluded that there were more e-cigarette explosion and burn injuries in the USA than estimated in previously published reports.
Dohnalek *et al.* [167] 2019	Harm	The authors, using information from a national database of emergency department visits, characterised the nature and frequency of **ENDS injuries** over a 10-year study period. Using archived information from the National Electronic Injury Surveillance System for the years 2008–2017, incidents of ENDS-related trauma were manually identified. A total of 49 incidents were recorded between the years 2008 and 2017, including 18 cases in 2017, 25 cases in 2016, 5 cases in 2015, and 1 case in 2013. There were no identified emergency department visits for an e-cigarette-related burn or explosion prior to 2013. Using statistical weights, the estimated annual national incidence is 835 cases. Most of the injuries were thermal burns. The primary location of injury was in the lower extremity, followed by the upper extremity and hand. The authors concluded that the study demonstrated a significant increase in the number of ENDS-related injuries over the study period, particularly in males under the age of 45 years.

4.2.3.2.7.2 Poisonings

Twenty-three papers reported on e-cigarette-related poisonings: 18 from the USA, 2 from Canada, and 3 from Europe (Spain, the UK, and 10 de-identified European Union member states). Summaries of these papers are presented in Table 30.

4.2.3.2.7.2.1 Canada

Two surveillance papers reported on e-cigarettes with adverse outcomes in the Canadian population.

The first is a report from the British Columbia Drug and Poison Information Centre,[177] and the second is a one-time survey of all paediatricians in Canada.[178]

The British Columbia data reported on the content of calls to the British Columbia Drug and Poison Information Centre between 2012 and 2017. [177] Over this 5-year period, 186 (76%) of 243 calls were related to exposures to e-cigarette devices, e-liquid, e-cigarette cartridges, and other associated paraphernalia. There was a six-fold increase in calls between 2012 and 2013, which then remained at a steady volume until 2017. Just under 45% of the calls related to exposures, predominantly accidental, in children under the age of 4 years. The predominant route of poisoning was through ingestion, and almost 48% of those exposed to poisoning reported symptoms.

The second paper also reported on e-cigarette-related adverse events, but additionally elicited information on a range of factors, including the nature of injury, treatment provided, and how products were accessed.[178] From 520 completed surveys, 220 adverse events were identified, 135 of which experienced adverse events due to product inhalation. Most inhalation-related adverse events occurred in males aged 15–19 years. The 85 adverse events arising from ingestion were mainly reported in children aged 1–4 years and resulted in gastric and respiratory symptoms. The cases involving younger patients accessed e-liquid at home, while the cases involving older patients accessed e-liquid in kiosks and stores.

4.2.3.2.7.2.2 Europe

Three surveillance papers based in Europe reported on e-cigarettes and their adverse outcomes. The three papers were from Spain,[179] and the UK,[180] and one paper covered 10 de-identified European Union member states.[181]

The findings from Spain noted an increase in the number of reported poisoning cases between January 2013 and April 2014, with a total of 64 cases, predominantly resulting after ingestion of e-liquid from refillable cartridges; 28% of these cases involved children.[179]

The UK had 278 reported queries to its poison centre between January 2008 and March 2016. There were few cases reported prior to 2012.[180] The cases reported in the 3-year period from 2013 to 2016 were mainly accidental in nature and asymptomatic. Of the intentional poisonings in the UK during this period, four out of five involved male adolescents. Symptoms, where present, were usually minor, consisting of vomiting, tachycardia, dysaesthesias, irritation, and increased creatine kinase.

Data from the national poison centres of 10 European Union member states were reported in a 2012–2015 European-based surveillance paper.[181] Of 277 e-liquid-related poisoning incidents, 71% were unintentional, and 67% occurred as a result of ingestion. The other exposure routes were inhalation, and ocular.

4.2.3.2.7.2.3 USA

The USA's 18 papers predominantly reported findings from the USA's National Poison Data System or its state-level centres (Arizona, California, Mississippi, Oregon, Texas, and Wisconsin). In total, there were 15 poison centre reports, 7 reporting at national level [182-185] [186] [187] [168] and 8 at state level. [188-190] [191-193] [194] [195]

Reporting was facilitated by the introduction of new unique codes to better capture e-cigarette-related information in September 2010.[182] American Association of Poison Control Centers (AAPCC)

generic codes 0200620 and 0200622 were developed to better classify e-cigarette-related information. [196]

The seven national-level reports covered five overlapping time periods between January 2001 and December 2018.[182-185 186 187 168] The incidences of poisoning reports were described using health determinants (age and sex), body part affected, geographic location (residence, work, state), mode of poisoning (ingestion, intravenous, topical absorption), and poisoning intent. For instance, poisonings in children aged under 5 years usually occurred by accidental ingestion in their own residence, as was highlighted in the American Association of Poison Control Centers 2014 paper.[183] In addition to the determinants of age and sex, the two additional principal determinants of poisoning were individual behaviours (e.g. suicidal intent) and the regulatory environment (determining the packaging requirements for e-liquids).

The eight state-level reports covered six states and time periods between 2009 and 2015.[188-190 191-193 194 195] In brief, some of the reporting characteristics were: poisoning intent, age, sex, vital signs, offending agent(s), medication(s) dosage, laboratory values, interventions, and outcomes. In addition, some state bodies undertook chemical analysis of the e-liquid. Among other issues, in a number of e-liquids, they identified differences between the printed and actual chemical composition of the examined products.

The most recent poisoning data were reported by Wang *et al.* (2019).[168] The authors described trends and characteristics of poisoning exposure cases involving e-cigarettes and e-liquids in the USA reported to the National Poison Data System by year (2010–2018) and by other characteristics. The annual number of e-cigarette exposure cases increased greatly between 2010 and 2014, reaching a peak of 3,742 in 2014, and then decreasing each year between 2015 and 2017. Between 2017 and 2018, the overall number of e-cigarette exposure cases increased again by 25% (from 2,320 in 2017 to 2,901 in 2018). Approximately two-thirds (64.8%) of all poisonings were in children aged under 5 years, 6.4% were children aged 5–17 years, and 8.3% were young adults aged 18–24 years. A small proportion of cases developed life-threatening symptoms (0.1%, equating to two or three cases per year), and cases with more serious medical outcomes tended to be exposed to a higher quantity of e-liquid or nicotine.

Recent findings from the USA's National Electronic Injury Surveillance System were also reported in two surveillance papers.[197 198] Data from 2013 to 2017 and from 2018 were used to calculate national estimates (95% CIs) of liquid nicotine-related poisonings among children aged under 5 years treated in USA hospital emergency departments. The number of e-liquid-related poisoning cases treated in hospitals increased from 181 (95% CI: 0–369) in 2013 to 1,736 (95% CI: 871–2,602) in 2015, and then decreased to 411 (95% CI: 84–738) in 2017, rising again to an estimated 885 (95% CI: 397–1,374) in 2018. The most common mode of poisoning was ingestion. Authors of the 2013–2017 estimates noted that at the time of reporting, the National Electronic Injury Surveillance System data did not include product codes specific to e-cigarettes or provide information on poisoning severity as a result of e-liquids; the authors were therefore required to use general keywords to capture these events and concluded that this might underestimate the population burden.

Finally, adverse events related to smoking cessation treatments and e-cigarettes in the United States Food and Drug Administration's Adverse Event Reporting System covering the period from April 2004 to December 2016 were reported by Motooka *et al.* (2018).[199] The total number of cases related to the administration of nicotine (after exclusion of duplicates) was 7,348,357. Adverse events were coded to the preferred terms of MedDRA Version 19.0. The number of adverse events (specifically nausea, nicotine dependence, and dizziness) for all forms of nicotine replacement therapy (NRT) was 1,673 for transdermally administered NRT, 1,016 for buccal NRT, 425 for oral NRT, and 56 for inhaled NRT. Regarding e-cigarettes, adverse events such as dizziness, dyspnoea, nausea, increased heart rate, and tremor were reported. For e-cigarettes, there were 27 cases where e-liquids were categorised as the primary suspect responsible for an adverse event. These included the adverse events of dizziness (n=4) and dyspnoea (n=4). There were two reported cases of each of the following: nausea, chest pain, increased heart rate, tremor, disorientation, cough, and wheezing. There was one reported case each of thermal burn, pulmonary oedema, and throat irritation. Other detected terms that were not currently included in MedDRA, but which were observed, included one case each of

altered visual depth perception, chills, device component issue, device deposit issue, device physical property issue, fear, headache, insomnia, lung disorder, malaise, migraine, product label issue, productive cough, panic reaction, sensation of heaviness, and seventh nerve paralysis, and two cases each of device malfunction and of pain.

Table 30 Surveillance papers on injuries and poisonings, presenting as poisonings, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
Canada		
Richmond *et al.*[178] 2018	Harm	The authors reported on symptoms related to inhalation in e-cigarette users in order to understand the relationship between hazardous materials in e-cigarettes and fluid (e-liquid) when inhaled or ingested, and the health risks in children and adolescents. The work explored the spectrum of **injuries related to e-cigarette exposure** among Canadian children and adolescents. A one-time survey was sent to all paediatricians in Canada. Information was collected on children and adolescents who presented with e-cigarette exposure (inhalation and ingestion cases) in the previous 12 months. Questions included the number of injuries and symptoms, in addition to age, sex, treatment setting, intentional e-cigarette use, and how the products were accessed. A total of 520 surveys were completed and returned, identifying 220 cases. Symptoms related to inhalation were present in 135 inhalation cases (43 unintentional, 92 intentional) and in 85 ingestion cases (35 unintentional, 50 intentional). For inhalation cases, most were males aged 15–19 years who sought treatment in an outpatient clinic/office for nausea/vomiting, cough, throat irritation, or acute nicotine toxicity. Most inhalation cases reported e-cigarette use 2–3 days/week, and that e-cigarettes were purchased from a mall kiosk/store. For ingestion cases, most were males aged 1–4 years presenting to an emergency department with nausea/vomiting, cough, or respiratory irritation. Younger cases accessed e-liquid at home, whereas older cases purchased it in a mall kiosk/store. E-liquid flavours reported to have been consumed were fruit, candy, and tobacco. The authors concluded that e-cigarettes, recently introduced into the North American market, are hazardous to children and adolescents.
Choi *et al.*[177] 2019	Harm	The authors conducted an observational case series study using records containing both coded fields and free-text narratives from the British Columbia Drug and Poison Information Centre for all calls involving **exposure to ENDS (poisonings)** received from 2012 to 2017. The authors described trends in exposures and exposed people, as well as clinical effects. A total of 243 calls were recorded for 186 unique exposures to e-cigarette devices, e-juice, e-cigarette cartridges, and other associated paraphernalia over the study period. Calls related to ENDS exposures increased nearly six-fold between 2013 and 2014 and did not subsequently decline. Exposures were most frequently documented in children aged 4 years or under (81 [43.5%]), with 58 cases (31.0%) occurring in 1- and 2-year-olds. 72 exposures (89%) in children aged 4 years or under were due to accidental ingestion. Adults aged 25 years or older called the poison centre following ENDS malfunctions (7 [23%]), spills (4 [13%]), and exposure to e-juice mistaken for other substances (4 [13%]). Of the 186 exposed people, 87 (46.8%) reported symptoms.
Europe		
Vardavas *et al.*[181] 2017	Harm	The authors reported on findings from 10 European Union member states on **e-cigarette exposures from national poison centres** between 2012 and March 2015. Of the 277 incidents reported, 71.3% were unintentional exposures (with e-cigarette refill vials responsible for 87.3% of the reported incidents). Two-thirds (67.5%) of all exposures occurred as ingestion of e-liquids, which was more frequent among children (≤5 years, 6–18 years) compared with adults (87.0% versus 59.3% versus 57.6%, respectively;

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
		p<0.001); exposure via the respiratory tract (5.4% versus 22.2% versus 22.2%, respectively; *p*<0.001) was more frequent among paediatric patients and adults, while ocular routes (2.2% versus 3.7% versus 11.4%, respectively; *p*=0.021) were more frequent among adults. Logistic regression analyses indicated that paediatric incidents (in children aged ≤5 years) were more likely to be through ingestion (adjusted odds ratio (AOR): 4.36; 95% CI: 1.87–10.18), but less likely to have a reported clinical effect (AOR: 0.41; 95% CI: 0.21–0.82).
Spain		
de la Oliva *et al.*[179] 2014	Harm	The authors reported on an audit of calls regarding cases of exposure to **e-cigarette-related poisons** between 1 January 2013 and 30 April 2014. Information was obtained from the database of the Spanish poison centre (Servicio de Información Toxicológica). They found 64 cases in which the recorded product involved was an e-cigarette, and observed an increase from 3 to 23 cases in the last quarter of 2013. Two-thirds of the cases registered involved the ingestion of liquid contained in the refillable cartridge; 28.1% were children (and 77.7% of those were aged under 2 years).
UK		
Ang *et al.*[180] 2018	Harm	The authors explored the effects of **e-liquid exposure** (poisoning) in the paediatric population from an analysis of all telephone enquiries to the UK's National Poisons Information Service. Cases of childhood e-liquid exposure from April 2008 to March 2016 were evaluated from the UK National Poisons Information Service database. The National Poisons Information Service received 278 enquiries regarding e-liquid exposure in children aged under 16 years between 2008 and 2016 involving 165 boys, 112 girls, and 1 of unknown sex. Most (222, 79.8%) were aged under 4 years. Most incidents were accidental and asymptomatic; no deaths occurred in this series, although complete follow-up data for individual cases are not available. Out of five intentional exposures, four involved male adolescents. When symptoms were present (63/278 cases), they were generally minor. The most common clinical features experienced by the children were vomiting (9.5%), tachycardia (2%), dysaesthesia (1%), irritation (1%), and increased creatine kinase (1%).
USA		
Cantrell Clark *et al.*[188] 2014a	Harm	The authors reported on findings from telephone calls to **poison** control centres in California between 2010 and 2013 on **exposures to nicotine solution**. There were 35 cases from 2010 to 2012, and 105 cases in 2013 alone. In 2013, exposure to nicotine refill solution was involved in 18% of all cases. Exposure in 10 children resulted in hospital evaluation for 7. Five adults mistakenly instilled nicotine refill solution instead of eyedrops into their eyes, resulting in considerable but transient irritation in each case. In addition, systemic symptoms of nicotine poisoning developed in three adults after they spilled nicotine refill solution on their skin.
Cantrell[189] 2014b	Harm	The second paper from these authors reports on findings from a state-wide poison system from 2010 to 2012. A total of 35 cases of **nicotine-related poisonings** were identified: 4 in 2010, 12 in 2011, and 19 in 2012. The patients' ages ranged from 8 months to 60 years. Reported symptoms were mild and transient. Five patients were evaluated in an emergency department and none were admitted. Product nicotine concentrations ranged from 4 to 30 mg/mL.

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
Chatham-Stephens *et al.*[182] 2014	Harm	The authors reported on findings from USA poison centres about human **e-cigarette-related poisonings** (exposure calls) from September 2010 (when new, unique codes were added specifically for capturing e-cigarette calls) through to February 2014. During the study period, poison centres reported 2,405 e-cigarette and 16,248 cigarette exposure calls from across the USA and its territories. E-cigarettes accounted for an increasing proportion of combined monthly e-cigarette and cigarette exposure calls, increasing from 0.3% in September 2010 to 41.7% in February 2014. A greater proportion of e-cigarette exposure calls than cigarette exposure calls came from healthcare facilities (12.8% versus 5.9%). Cigarette exposures were primarily among persons aged 0–5 years (94.9%); e-cigarette exposures, on the other hand, occurred among persons aged 0–5 years in 51.1% of cases and among persons aged over 20 years in 42.0% of cases. E-cigarette exposures were more likely than cigarette exposures to be reported as inhalations (16.8% versus 2.0%), eye exposures (8.5% versus 0.1%), and skin exposures (5.9% versus 0.1%), and less likely than cigarette exposures to be reported as ingestions (68.9% versus 97.8%). Among the 9,839 exposure calls with information about the severity of adverse health effects, e-cigarette exposure calls were more likely than cigarette exposure calls to report an adverse health effect after exposure (57.8% versus 36.0%).
Vakkalanka *et al.*[183] 2014	Harm	The authors reported on trends in **e-cigarette-related poisonings** reported to USA poison centres between 1 June 2010 and 30 September 2013. In addition to the trends in exposures over time, trends in demographics, geographic characteristics, clinical effects and outcomes, management site, and exposure route were also assessed. A total of 1,700 exposures were reported to poison centres during this time. The most frequently affected age groups were children aged under 5 years, with 717 (42.2%) exposures, and adults aged 20–39 years, with 466 (27.4%) exposures. Temporal trends showed an increase of 1.36 exposures per month (95% CI; 1.16–1.56) from June 2010 through December 2012, after which the average number of exposures increased by 9.6 per month (95% CI; 8.64–10.55) between January and September 2013. Most patients who were followed up on reported that they had only minor effects. The majority of exposures to e-cigarette devices and components occurred in children aged under 5 years due to accidental exposure.
Forrester[190]. 2015	Harm	The author reported findings from Texas poison centres from January 2010 to June 2014. Cases of **e-cigarette-related poisonings** among patients aged 5 years or under were reported. Of 203 exposures, 2 cases were reported in 2010, 5 in 2011, 20 in 2012, 70 in 2013, and 106 between January and June 2014. 51% of the patients were male; 32% of the patients were aged 1 year, and 42% were aged 2 years. 96% of the exposures occurred at the patient's own residence. The exposure routes were ingestion (93%), dermal (11%), ocular (3%), and inhalation (2%). 58% of the patients were managed on site. Of the patients seen at a healthcare facility, 69% were treated or evaluated and released. 11% of the exposures were serious. The most commonly reported clinical effects were vomiting (24%), drowsiness/lethargy (2%), and cough/choking (2%). The author found e-cigarette exposures involving young children reported to poison centres to be increasing, with exposures most likely to involve patients aged 2–3 years, occur at the child's own residence, and occur by ingestion.
LoVecchio *et al.*[191] 2015	Harm	The authors conducted a retrospective medical record review of **e-cigarette-related poisoning** calls to the Arizona Poison Control Centre in order to evaluate trends in exposures over time and patient demographics, and to further characterise outcomes following e-cigarette exposure. Data from cases of e-cigarette exposures called into the Arizona Poison Control Centre between 1 January 2012 and 31 December 2014 were used for analysis. Data

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
		collected included case number, age, sex, vital signs, intent, offending agent(s), medication(s), dosage, laboratory values, interventions, and outcomes. All[191] patients were followed until the cessation of symptoms or were evaluated via a 1-hour telephone follow-up if asymptomatic. During the study period, 100 patients met the inclusion criteria. E-cigarette exposure calls increased annually, with 10 total reported exposures in 2012, 24 in 2013, and 66 in 2014. Children aged 5 years or under accounted for 52.0% of total exposure calls (range: 40.0%–54.2%). All patients were asymptomatic or reported mild symptoms, including vomiting, nausea, and dizziness. Poison dose information was not obtained, so the mild clinical symptoms may reflect low exposure doses.
Ordonez *et al.*[192] 2015	Harm	The authors reported on **e-cigarette-related poisonings** reported to Texas poison centres between 2009 and February 2014. Of 225 total exposures, 2 were reported in January 2009, 6 in 2010, 11 in 2011, 43 in 2012, 123 in 2013, and 40 through February 2014. 53% (n=119) occurred among individuals aged 5 years or under, 41% (n=93) occurred among individuals aged 20 years or over, and 6% (n=13) occurred among individuals aged 6–19 years. 50% were female. The route of exposure was ingestion in 78% of cases. 87% of the exposures were unintentional, and 5% were intentional. The exposures occurred at the patient's own residence in 95% of the cases. The clinical effects reported most often were vomiting (20%), nausea (10%), headache (4%), ocular irritation (5%), dizziness (5%), and lethargy (2%).
Valentine *et al.*[193] 2016b	Harm	The authors reported on findings from the Mississippi State University Social Science Research Center. Surveys assessed e-cigarette use among Mississippi adolescents and adults. The centre provided data on reported cases of **e-cigarette-related poisonings**. From 2010 to 2014, current e-cigarette use increased from 0.6% to 6.7% among middle school students, from 1.2 % to 10.1% among high school students, and from 0.2% to 6.8% among adults. There were no reported cases of e-cigarette-related poisonings in 2010, 2011, or 2013. There was one case in 2012, 26 in 2014, and 17 in 2015.
Chatham-Stephens *et al.*[184] 2016	Harm	The authors compared findings from **poison** centres from September 2010 through December 2014, reporting data on monthly counts and demographics, exposure, and health effects from calls about **e-cigarettes and conventional combustible tobacco cigarettes**. Monthly e-cigarette calls increased from 1 in September 2010 to a peak of 401 in April 2014, and declined to 295 in December 2014. Monthly conventional combustible tobacco cigarette calls during the same period ranged from 302 to 514. E-cigarette calls were more likely than conventional combustible tobacco cigarette calls to report adverse health effects, including vomiting, eye irritation, and nausea. Five e-cigarette calls reported major health effects, such as respiratory failure, and there were two deaths associated with e-cigarette calls.
Kamboj *et al.*[185] 2016	Harm	The authors reported on **poisonings** associated with **nicotine and tobacco products** among children aged 6 years or under from the USA's National Poison Data System data from January 2012 through April 2015. There were 29,141 calls for nicotine and tobacco product exposures among children aged 6 years or under, averaging 729 child exposures per month. Tobacco cigarettes accounted for 60.1% of exposures, followed by other tobacco products (16.4%) and **e-cigarettes** (14.2%). The monthly number of exposures associated with e-cigarettes increased by 1,492, or 9%, over the study period. Children aged under 2 years accounted for 44.1% of e-cigarette exposures, 91.6% of cigarette exposures, and 75.4% of other tobacco exposures. Children exposed to e-cigarettes had 5.2 times higher odds of a healthcare facility admission and 2.6 times higher odds of having a severe

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
		outcome than children exposed to cigarettes. One death occurred in association with a nicotine liquid exposure.
Weiss *et al.*[194] 2016	Harm	The authors reported on **tobacco cigarette and e-cigarette-related poisoning** calls to the Wisconsin Poison Center from 1 January 2010 through 10 October 2015. The authors compared cigarette and e-cigarette exposure calls by several characteristics. During the study period, 98 e-cigarette exposure calls were reported, and the number of annual e-cigarette exposure calls increased approximately 17-fold, from 2 to 35. During the same period, 671 single-exposure cigarette calls were reported, with stable annual call volumes. The majority of e-cigarette exposure calls were associated with children aged 5 years or under (57/98, 58.2%) and adults aged 20 years or over (30/98, 30.6%). Cigarette exposure calls predominated among children aged 5 years or under (643/671, 95.8%). The authors concluded that the frequency of e-cigarette exposure calls had increased and was highest among children aged 5 years or under and adults aged 20 years or over.
Wang *et al.*[186] 2017	Harm	Using data from the National Poison Data System from 1 January 2001 to 31 October 2016, the authors analysed data on **tobacco-related poison** exposure calls involving children aged under 5 years. From 2001 to 2016, there were 123,876 calls involving young children. During the study period, calls increased for most product types; **e-cigarette**-related calls increased from 7 in 2010 to 2,558 in 2015. In calls with information on level of care (92.2%), 278 children were admitted to an intensive care unit, 497 were admitted to a hospital non-critical care unit, and 19,834 were treated and released. The authors concluded that tobacco-related poison events commonly occur in the USA and have serious health consequences, and that this likely represents a small portion of actual tobacco-related poisoning events due to underreporting.
Govindarajan *et al.*[187] 2018	Harm	The authors reported on **liquid nicotine poisoning** data from the USA's National Poison Data System for January 2012 to April 2017. Of the 8,269 liquid nicotine exposures among children aged under 6 years, most (92.5%) were exposed through ingestion and 83.9% were aged under 3 years. Among children exposed to liquid nicotine, 35.1% were treated and released from a healthcare facility and 1.4% were admitted. The annual exposure rate per 100,000 children increased substantially, from 0.7 in 2012 to 10.4 in 2015, and subsequently decreased to 8.3 in 2016. The authors reported that among states without a pre-existing law requiring child-resistant packaging for liquid nicotine containers, there was a significant decrease in the mean number of exposures during the 9 months before compared with during the 9 months after the federal child-resistant packaging law went into effect, averaging 4.4 (95% CI: -7.1 to -1.7) fewer exposures per state after implementation of the law. The authors concluded that decreased paediatric exposures to liquid nicotine after January 2015 may, in part, be attributable to legislation requiring child-resistant packaging.
Motooka *et al.*[199] 2018	Harm	The authors reported on the number of **adverse events related to smoking cessation treatments and e-cigarettes** in the United States Food and Drug Administration's Adverse Event Reporting System covering the period from April 2004 to December 2016. The total number of cases related to the administration of nicotine (after exclusion of duplicates) was 7,348,357. Adverse events were generated according to the preferred terms of MedDRA Version 19.0. The numbers of adverse events (specifically nausea, nicotine dependence, and dizziness) for all forms of NRT were 1,673 for transdermal, 1,016 for buccal, 425 for oral, and 56 for respiratory administration. For e-cigarettes, 27 cases of primary suspect adverse events were reported; these included 4 cases each for the adverse events of dizziness and dyspnoea. The reported numbers of cases of nausea, chest pain, increased heart rate,

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
		tremors, disorientation, cough, and wheezing were two for each category. The reported numbers of cases of thermal burn, pulmonary oedema, and throat irritation were one for each category. Other detected terms which were not currently included in MedDRA but which were observed included: altered visual depth perception (1), chills (1), device component issue (1), device deposit issue (1), device malfunction (2), device physical property issue (1), fear (1), headache (1), insomnia (1), lung disorder (1), malaise (1), migraine (1), pain (2), product label issue (1), productive cough (1), panic reaction (1), sensation of heaviness (1), and seventh nerve paralysis (1).
Chang[197] 2019a	Harm	The author used National Electronic Injury Surveillance System data from 2013 to 2017 to calculate national estimates (95% CI) of **poisoning incidents related to e-liquid nicotine exposure**. From 2013 to 2017, an estimated 4,745 poisoning cases related to e-liquids among children aged under 5 years were treated in USA hospital emergency departments; the number of cases increased from 181 (95% CI: 0–369) in 2013 to 1,736 (95% CI: 871–2,602) in 2015, and then decreased to 411 (95% CI: 84–738) in 2017. Most of the cases were treated and released; 4.1% were admitted to the hospital. The most common route of exposure was through ingestion (96.9%), and 2.6% of the cases were through dermal exposure. The highest amount of e-liquids or nicotine ingested was difficult to assess as the measures assessed were not standardised. For example, 118.2 mL was the highest volume, and 100 mg was the highest weight. The most common symptoms related to nicotine poisoning were nausea and vomiting (63.6%). The author noted that at the time of reporting, since the National Electronic Injury Surveillance System data did not include product codes specific to e-cigarettes or provide information on poisoning severity, the author was required to use general keywords to capture these events, which might underestimate the population burden.
Chang[198] 2019b	Harm	The author used 2018 National Electronic Injury Surveillance System data to generate national estimates (95% CI) of ENDS **liquid nicotine-related poisonings** among children aged under 5 years who were treated in USA hospital emergency departments. In 2018, an estimated 885 (95% CI: 397–1,374) poisoning cases that were related to liquid nicotine among children aged under 5 years were treated in USA hospital emergency departments, which was a non-statistically significant increase from 2017 (411 poisoning cases, 95% CI: 84–738). The most common route of exposure was through ingestion (99.4%). Most cases were treated and released from the hospital (90.0%), 8.9% of the cases left the hospital without being seen, and 1.1% of the cases were treated and admitted to the hospital.
Hughes *et al.* [195] 2019b	Harm	The authors undertook an examination of records of calls to a single poison centre (in Oregon) from 1 July 2014 to 31 December 2017. For all calls that involved **e-cigarette devices or e-liquid**, a data collection instrument was filled out by the specialist in poison information; 265 cases were identified, including 193 children and 72 adults. The majority of both paediatric (72%; n=139) and adult (61%; n=44) exposures involved e-liquid refill containers or fluid. 56% (n=108) of paediatric **exposures** involved ingestion of e-liquid. Although children who ingested e-liquid received only a small amount, initial symptoms were evident in 32% (n=35) of cases. Children who did not ingest or inhale the products were less likely to develop toxicity. Only two children who were asymptomatic on initial call became symptomatic on follow-up. Most patients' symptoms resolved within 4 hours. 71 specific products/brands were identified, with nicotine concentrations ranging from 0 mg/mL to 60 mg/mL, and one product containing 3000 mg in a single bottle. A variety of flavours were identified, including several with names that may be attractive to toddlers or adolescents. E-cigarette exposures tend

Author(s), year	Possible benefit or harm	Surveillance papers on injuries and poisonings presenting as poisonings
		to produce irritant effects from topical exposures and nicotine toxicity from ingestions, as well as from some dermal and "sucking" toddler exposures.
Wang *et al.* [168] 2019a	Harm	The authors analysed **poisoning exposure cases** involving **e-cigarettes and e-liquids** from the National Poison Data System from 2010 to 2018. The annual number of e-cigarette exposure cases increased greatly between 2010 and 2014, reaching a peak of 3,742 in 2014, and then decreasing each year between 2015 and 2017. Between 2017 and 2018, the overall number of e-cigarette exposure cases increased by 25.0% (from 2,320 to 2,901). Approximately two-thirds (64.8%) of all poisonings were in children aged under 5 years, 6.4% were in children aged 5–17 years, and 8.3% were in young adults aged 18–24 years. A small proportion of cases developed life-threatening symptoms (0.1%); cases with more serious medical outcomes tended to be exposed to a higher quantity of e-liquid or nicotine. The authors concluded that annual declines in e-cigarette exposure cases between 2015 and 2017 did not continue in 2018

4.2.3.2.8 Exposure to e-cigarette toxins: surveillance papers

There was one surveillance paper on secondary exposure to e-cigarettes (Table 31). Notifications received by the United States Food and Drug Administration Center for Tobacco Products between January 2012 and December 2014 reported 40 events involving non-e-cigarette users.[169] Thirty-five reports related to mainly indoor passive aerosol exposure. Respiratory symptoms, the most common adverse events, included asthma exacerbations, bronchitis, cough, difficulty breathing, and pneumonia. Additional symptoms included eye irritation, headache, nausea, throat irritation, dizziness, and racing or irregular heart rate. Of the reports providing information about pre-existing conditions, just under half indicated a history of respiratory disease or allergy. The four reports on children included an infant death, burns in a 3-year-old following an e-cigarette explosion, breathing problems in a 3-year-old, and 'raspy' voice in a 4-year-old after passive aerosol exposure.

Table 31 Surveillance papers on exposure to e-cigarette toxins, benefits or harms

Author(s), year	Possible benefit or harm	Surveillance papers on exposure to e-cigarette toxins
Durmowicz *et al.*[169] 2015	Harm	The authors reported on notifications received by the United States Food and Drug Administration Center for Tobacco Products between 1 January 2012 and 31 December 2014 associated with e-cigarettes, but only in non-users. Of the 136 reports related to **e-cigarette adverse events**, 40 involved non-users. 35 reports were related to passive aerosol exposure (typically in indoor spaces). Respiratory symptoms (n=26, including 2 children) were most common and included asthma exacerbations, bronchitis, cough, difficulty breathing, and pneumonia. Additional passive aerosol exposure symptoms included eye irritation (n=8), headache (n=8), nausea (n=6), sore throat/irritation (n=6), dizziness (n=5), and racing/irregular heart rate (n=5). 11 reports identified recurrent problems associated with repeat exposure, and 6 reports described adverse events in multiple individuals. Six cases reported seeking medical attention; three of these cases reported prescription of medications, two reported self-treatment, and one reported hospitalisation. Of 27 reports providing information about pre-existing conditions, 11 indicated a history of respiratory or allergic conditions and 9 of those adverse events may have been related to the underlying condition. The remaining five non-user reports included three reports of burns (due to contact with an overheated device [n=2] and to device explosion [n=1 child] while recharging), one report of lip cheilitis (after kissing an e-cigarette user), and one report of infant death after choking on an e-liquid cartridge. Most non-user reports (n=36) were in adults.

4.2.3.2.9 Other outcomes: surveillance papers

There were no surveillance papers on the relationship between e-cigarettes and other outcomes.

4.3 Observational epidemiological studies: e-cigarettes

Incidents of mainly harms associated with e-cigarette devices or e-liquids were reported in 110 papers. Stratification by research design allowed us to categorise the papers into 86 cross-sectional surveys, 2 case-control studies, and 22 longitudinal cohort studies. The sample sizes ranged from 20 to 486,303.

The authors of the 86 cross-sectional surveys described the association of e-cigarette devices or e-liquids with mainly health-related harms.

The authors of the two case-control studies identified two harms probably associated with either e-cigarette devices or e-liquids.

The 22 longitudinal cohort studies reported data on exposure to e-cigarette devices or e-liquids at baseline and followed up on the incidence of outcomes observed in the same individuals during subsequent timepoints.

The summary tables for cross-sectional surveys, case-control studies, and longitudinal cohort studies are presented under the adapted Academies of Sciences' headings in Sections 4.3.1, 4.3.2, and 4.3.3. These summary tables present details of the authors, study objectives, and concluding summary findings. For cross-sectional surveys and longitudinal cohort studies, tables with additional details are presented in Appendices 3 and 4.

4.3.1 Cross-sectional surveys: e-cigarettes

4.3.1.1 Study characterisation: e-cigarettes

In the 86 cross-sectional surveys, the investigator measured the exposures (e-cigarette and/or e-liquid) and the outcome (benefit or harm) in the study participants at the same timepoint.[27] These surveys are very useful for describing the prevalence of an outcome such as a harm or benefit in the included population. However, cross-sectional surveys require adequate sample sizes in order to estimate prevalence. The limitations of cross-sectional surveys are that they cannot establish a temporal sequence and they have difficulty controlling for the influence of confounding factors on the outcome of interest.

The cross-sectional surveys were completed on populations living in 17 countries, but the majority were from the USA. The countries were: Egypt (n=1), France (n=1), Greece (n=1), Hong Kong China (n=1), Hungary (n=1), Indonesia (n=1), Italy (n=1), South Korea (n=7), Malaysia (n=1), Poland (n=3), Saudi Arabia (n=8), Romania (n=1), Spain (n=1), Sweden (n=1) Turkey (n=1), the UK (n=1), and the USA (n=51). Two studies included populations from across Europe and another two studies included populations from across the world. The surveys were published between 2010 and 2019. The sample sizes ranged from 20 to 486,303.

A significant minority of cross-sectional survey papers were on dependence and abuse liability (21 out of 86) and respiratory diseases (21 out of 86). The number of cross-sectional survey papers categorised under the adapted Academies of Sciences' framework were: 21 under dependence and abuse liability, 5 under cardiovascular diseases, 5 under cancers, 21 under respiratory diseases, 14 under oral diseases, 9 under exposure to e-cigarette toxins, and 11 under other outcomes, which reported on endocrine outcomes, ophthalmic outcomes, and passive exposure outcomes. There were no cross-sectional survey papers under the headings 'developmental and reproductive effects' or 'injuries and poisonings'.

The summary tables for cross-sectional surveys are presented under the adapted Academies of Sciences' headings in Sections 4.3.1.2.1 to 4.3.1.2.9. These summary tables present the authors, study objectives, and concluding summary findings. For cross-sectional surveys, tables with additional details are presented in Appendix 3.

4.3.1.2 Harms, harm reduction, and benefits: e-cigarettes

The harms associated with e-cigarette use identified under the dependence and abuse liability heading and investigated in cross-sectional surveys were: high level of dependence on e-cigarettes, depression, suicidality, sleep disturbance, and use by young people as a method of weight control. The harm identified under cardiovascular diseases was the higher level of activation of the inflammatory signaling network underlying acute cardiac ischaemia in e-cigarette users compared to non-users. The presence of carcinogens for lung, oral, and oesophageal cancers was identified in e-cigarette users under the cancers heading. In support of the possible link between cancers and tissue damage in e-cigarette users, metals, volatile organic compounds, and other toxins were identified as contributing constituents. Some of the metals and volatile organic compounds identified in e-cigarettes were not in conventional tobacco cigarette smoke. A number of respiratory conditions were associated with e-cigarettes, including lung injury, exacerbation of asthma in active and passive users, and exacerbation of chronic obstructive pulmonary disease. Signs of possible future respiratory diseases in e-cigarette users were also described; specifically, sputum abnormalities, and genes displaying decreased expression. Under the oral diseases heading, plaque, caries, periodontal diseases, and markers for oral infection were identified in e-cigarette users. Passive or third-hand nicotine intake was also identified among infants in neonatal units.

A number of cross-sectional surveys identified that e-cigarettes were less harmful than conventional tobacco cigarettes. For example, one cross-sectional survey paper showed that individuals' dependence level on e-cigarettes was lower than their dependence level on tobacco cigarettes. One other cross-sectional survey demonstrated that while there is inflammation of the signalling network underlying acute cardiac ischaemia in e-cigarette users, such inflammation is lower than that found in smokers. Additionally, while carcinogens are present in e-cigarette users' body fluids, the levels are lower than those found in smokers, and e-cigarette users excrete lower levels of polycyclic aromatic hydrocarbon biomarkers in their urine than tobacco cigarette smokers. Two cross-sectional surveys showed that the extent of caries and periodontal disease was lower in e-cigarette users than in tobacco cigarette smokers, but this finding is not supported by other cross-sectional surveys. Finally, one cross-sectional survey paper found that the effects of e-cigarettes on the voice were mild when compared with voice effects in tobacco cigarette smokers.

The only benefits of e-cigarettes identified in cross-sectional surveys was the possibility of e-cigarette use for smoking cessation or reduction.

4.3.1.2.1 Dependence and abuse liability: cross-sectional surveys

Twenty-one cross-sectional survey papers reported measures of illness, behaviours, and personality traits associated with dependence and abuse liability (Table 32). Some papers included measures of mental health and well-being, such as measures of anxiety sensitivity, depression, suicidality, and pain severity. The surveys also measured the prevalence of e-cigarette use among people with mental health conditions (such as anxiety, depression, emotional disorder, attention deficit disorder, bipolar disorder, and schizophrenia). Some cross-sectional survey papers measured e-cigarette-related behavioural outcomes (such as impact on sleeping patterns) and dependency (measure of frequency of e-cigarette use, patterns of use, assessment of dependence, and urinary cotinine levels in body fluids). Other outcomes examined in cross-sectional survey papers included tobacco cigarette use and marijuana use, weight status, and appetite control.

Five cross-sectional survey papers found support for e-cigarette use in cigarette reduction, cessation, and dependence levels. The first paper concluded that experienced e-cigarette users stated that initiating e-cigarette use helped them to quit or reduce their conventional smoking, which they believe reduced their health risks.[200] Survey respondents who used e-cigarettes acknowledged that more research is needed in order to understand the safety and long-term effects of e-cigarette use; they also reported that current effects experienced by them included dry mouth and lack of reliability of e-cigarette products. The second paper reported that e-cigarettes were mostly used by respondents to avoid the harm associated with smoking. In this survey, high levels of nicotine were used at initiation, and users subsequently tried to reduce nicotine consumption, with only a small minority moving to non-nicotine liquids.[201] The third paper concluded that nicotine levels appear to

play an important role in achieving and maintaining cessation of smoking conventional tobacco cigarettes in a group of motivated smokers.[202] The fourth survey paper determined that some e-cigarette users were dependent on nicotine-containing e-cigarettes, but that these products were less addictive than conventional tobacco cigarettes.[203] The final paper reported that dual users smoked significantly fewer cigarettes and were more likely to have a psychiatric history.[204]

By contrast, another four cross-sectional surveys questioned cigarette reduction, cessation, and dependence levels associated with e-cigarette use. The first cross-sectional survey paper reported that its results did not suggest that e-cigarette use was associated with a reduction in cigarette consumption to less than one pack per day.[205] Current use of conventional tobacco cigarettes and e-cigarettes was associated with quit attempts in the past 12 months, and a self-reported likelihood of future tobacco cessation. However, e-cigarette use was not associated with confidence to quit in the next month, cigarette packs smoked per day, or salivary cotinine levels. The second paper concluded that e-cigarette users had higher average nicotine dependence levels than conventional cigarette users; nicotine dependence levels were titrated to years of e-cigarette use and the concentration of nicotine in the e-liquid used.[206] The third paper determined that adolescents who used pod products reported more signs of nicotine dependence than non-pod users.[207] Positive responses to dependence questions were supported by higher urinary cotinine levels. The fourth paper reported that nicotine dependence levels, measured using the Fagerström Test for Nicotine Dependence, were more than two times higher among e-cigarette users compared to traditional tobacco smokers. [208] Similarly, among dual users, nicotine dependence levels were higher when using an e-cigarette compared to when using conventional tobacco cigarettes. The final paper concluded that dual users (those who used both e-cigarettes and conventional tobacco cigarettes) were more likely to be white, be younger, have above a high school education, and have a psychiatric history. Dual users also smoked significantly fewer cigarettes and had lower levels (rather than none) of the carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol.

Six papers reported a harmful association between e-cigarettes and mental health. One paper concluded that, after controlling for covariates, having a chronic mental illness significantly increased the likelihood of both trying an e-cigarette and being an e-cigarette user.[209] One study reported that, after adjusting for covariates, a nationally representative sample of adolescents who used e-cigarettes only, marijuana only, or both e-cigarettes and marijuana had significantly poorer mental health outcomes (depression and suicidality) when compared with those who did not use such substances.[210] A further three studies supported the association between e-cigarettes and suicidal behaviour and/or depression.[211] [212] One study reported that dual use of e-cigarettes with another product was associated with higher depressive symptoms.[213] One paper concluded that there needs to be further investigation into anxiety sensitivity and pain severity in the context of e-cigarette use, as there may be a benefit to screening for and clinically addressing these factors in order to help offset the effects of e-cigarette use.[214]

Two studies examined the topic of e-cigarettes and body weight. A single study concluded that the existing relationship between obesity and increased cigarette smoking may extend to e-cigarette use among young adults.[215] Another paper described how a subset of adolescents had reported using flavoured e-liquids to lose weight, and that these adolescents reported vaping more frequently than their counterparts, raising concerns about increased nicotine exposure.[216]

Three papers reported a harmful association between e-cigarettes and sleep patterns. The first paper found that dual use of e-cigarettes with conventional tobacco had the highest risk for causing sleep disruption; nicotine or coughing were considered the causal agent and mechanism, respectively. [217] The second paper concluded that conventional cigarette and e-cigarette users reported significantly more sleep difficulties than never users, and that e-cigarette users reported greater use of sleep medication than did combustible cigarette users.[218] The third paper concluded that e-cigarette and dual-product use are significantly associated with greater odds of reporting sleep-related complaints among adolescents.[219]

One paper concluded that the findings of their research suggest that e-cigarette use increased as self-perceived health decreased [220]

Table 32 Cross-sectional survey papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		Smoking reduction, smoking cessation, and nicotine levels
Farsalinos *et al.* [202] 2013b	Benefit	The authors described the **nicotine levels used in order to achieve smoking cessation**, as well as the reported benefits, associated side effects, and estimation of e-cigarette dependence, compared with tobacco cigarette dependence. *Comparative groups* E-cigarettes users themselves (former smokers) The authors concluded that nicotine levels appear to play an important role in achieving and maintaining smoking cessation in the group of motivated subjects studied. High-nicotine-containing liquids were used, but few mild and temporary side effects were reported. The authors concluded that regulatory proposals should consider the pragmatic use patterns of e-cigarettes, especially in consumers who have completely substituted tobacco cigarettes with e-cigarettes.
Farsalinos *et al.* [201] 2014c	Less harmful than conventional combustible tobacco cigarettes	The authors described the characteristics, perceived **side effects, and benefits of e-cigarettes.** *Comparative groups* E-cigarettes themselves (with detail on device type, as occasional users) Conventional combustible tobacco cigarette smokers • Former smokers • Never smokers • Current smokers They concluded that e-cigarettes are mostly used to avoid the harm associated with smoking. They noted that e-cigarettes can be effective even in highly dependent smokers, and that they are used as long-term substitutes for smoking. High levels of nicotine are used at initiation; subsequently, e-cigarette users try to reduce nicotine consumption, with only a small minority using non-nicotine liquids. Side effects are minor and health benefits are substantial, especially for those who completely substitute tobacco cigarettes with e-cigarettes.
Etter *et al.* [203] 2015	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **dependence level** in users of **e-cigarettes, nicotine gum, and tobacco cigarettes.** *Comparative groups* E-cigarettes themselves (former smokers) Conventional combustible tobacco cigarette smokers • Former smokers • Daily smokers • Occasional smokers Nicotine gum users History of other types of tobacco use (pipe smokers, cigar smokers, smokeless and chewing tobacco, hookah use) They concluded that some e-cigarette users were dependent on nicotine-containing e-cigarettes, but that these products were less addictive than tobacco cigarettes. E-cigarettes may be as addictive as or less addictive than nicotine gums, which themselves are not very addictive.
Baweja *et al.* [200] 2016	Benefit	The authors reported on the **experiences, satisfaction, opinions, and preferences of e-cigarette users.** *Comparative groups* E-cigarettes themselves (former smokers) Conventional combustible tobacco cigarette smokers • Former smokers • Current smokers Smokers, who use other tobacco products They concluded that experienced e-cigarette users stated that initiating e-cigarette use helped them to quit or reduce their conventional smoking, which they believed reduced their health risks. In comparison to cigarette smoking, e-cigarette users reported using their e-cigarette more times per day, but with fewer puffs than on conventional combustible tobacco cigarettes at each use time. E-cigarette

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		users acknowledged that more research is needed in order to understand the safety and long-term effects of use. Finally, the e-cigarette users mentioned dry mouth as a common side effect and they also noted common problems with the reliability of e-cigarettes.
Comiford *et al.*[205] 2018	Harm	The authors reported on the relationship between **e-cigarette use and smoking-related measures** (salivary cotinine levels) among American Indians who smoked. *Comparative groups* E-cigarettes users themselves as former smokers E-cigarettes users themselves as never smokers E-cigarettes users themselves as dual or poly product uses (themselves and one or more tobacco product) Conventional combustible tobacco cigarette users (current) The results did not suggest that e-cigarette use is associated with a reduction of cigarette consumption to less than one pack per day. Current use of cigarettes and e-cigarettes was associated with quit attempts in the past 12 months and a self-reported likelihood of future tobacco cessation, and that this may be an indication that e-cigarette use may signify a greater interest in smoking cessation. However, e-cigarette use was not associated with confidence to quit in the next month, cigarette packs smoked per day, or salivary cotinine levels.
Johnson *et al.*[206] 2018	Harm	The authors reported on the relationship between characteristics of **e-cigarette usage and Fagerström Test for Nicotine Dependence outcome scores**, specifically scores on nicotine dependence. *Comparative groups* E-cigarettes users themselves only (current) E-cigarette users themselves who were former smokers (current) E-cigarette users themselves who were conventional combustible tobacco cigarette smokers and/or water pipe users (current) The authors concluded that e-cigarette users can have higher average nicotine dependence levels than conventional combustible tobacco cigarette users. They noted that the length of e-cigarette use (<1 year versus >1 year) and the level of nicotine used in e-cigarette liquid (none versus any level of nicotine) were significantly associated with the Fagerström Test for Nicotine Dependence scores. They also noted that those who used e-cigarette fluid with no nicotine had lower scores than those who used fluids that contained nicotine.
Piper *et al.*[204] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between completed **baseline assessments of demographics, tobacco use, and dependence**. They also provided details of breath samples for carbon monoxide (CO) assay and urine samples for cotinine, 3-hydroxycotinine (3HC), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL, a carcinogen) assays. *Comparative groups* E-cigarettes users themselves Conventional combustible tobacco cigarette smokers (current, ≥ 5 cigarettes per day for 6 months) Dual users (e-cigarettes and conventional combustible tobacco cigarette users) The authors concluded that dual users were more likely to have a psychiatric history. Dual users also smoked significantly fewer cigarettes and had lower levels of NNAL (a carcinogen), but they did not differ from exclusive smokers in terms of carbon monoxide or cotinine levels, suggesting that they supplemented their nicotine intake via e-cigarettes.
Boykan *et al.*[207] 2019	Harm	The authors reported on differences in urinary cotinine levels in **pod versus non-pod** e-cigarette users. In addition, they assessed **dependence levels** in a subset of the original population. *Comparative groups* E-cigarettes themselves (as past-week pod users) E=cigarettes themselves (as past-week non pod users)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		The authors concluded that adolescents who used pod products showed more signs of nicotine dependence than non-pod users. Positive responses to dependence questions were reflected in higher urinary cotinine levels.
Jankowski *et al.*[208] 2019	Harm	The authors assessed **patterns of e-cigarette use and compared nicotine dependence** among cigarette and e-cigarette users in a group of highly educated young adults. *Comparative groups* E-cigarettes themselves Conventional combustible tobacco cigarette users (current users) Dual users (e-cigarette and conventional combustible tobacco cigarette users) The authors concluded that the nicotine dependence levels measured with the Fagerström Test for Nicotine Dependence were more than two times higher among e-cigarette users than among traditional tobacco smokers. Similarly, among dual users, nicotine dependence levels were higher when using an e-cigarette compared to using conventional combustible tobacco cigarettes. Habits and behaviours associated with the use of e-cigarettes did not differ significantly between exclusive e-cigarette users and dual users of e-cigarettes and conventional combustible tobacco cigarettes. The findings suggest that e-cigarettes may have a higher addictive potential than smoked cigarettes among young adults.
		Mental health
Bandiera *et al.*[211] 2016	Harm	The authors reported on the relationship between **tobacco and nicotine product use and depressive symptoms.** *Comparative groups* E-cigarettes themselves (current users) Conventional combustible tobacco cigarette users (current users) Other tobacco product current users (hookah, cigar, smokeless tobacco) The authors reported that e-cigarettes were the only alternative tobacco product that were uniquely associated with depressive symptoms, and that the association was significant even after controlling for current cigarette use, sociodemographic characteristics, and current use of three other three alternative tobacco products tested.
Bianco *et a.l*[209] 2019	Harm	The authors reported on the **rates of e-cigarette use among adults with a chronic mental illness** (classified as depression, anxiety, emotional disorder, or ADD, bipolar disorder, schizophrenia, other disorders). *Comparative groups* E-cigarettes themselves (ever to daily use) Conventional combustible tobacco cigarette users (current users with data on daily and some days use) Never-e-cigarette users The authors noted that previous trial of an e-cigarette is more likely in a person with depression, anxiety, or an emotional problem (odds ratio (OR): 2.84). Trying an e-cigarette is more likely in a person with ADD, bipolar disorder, schizophrenia, or other disorder (OR: 2.47). Regular e-cigarette use is more likely in a person with depression, anxiety, or an emotional problem (OR: 2.69). Regular e-cigarette use is more likely in a person with ADD, bipolar disorder, schizophrenia, or other disorder (OR: 3.02). However, as the temporary path of mental health diagnosis and e-cigarette uptake was not specified, the reported relationship must be viewed as cross-sectional in nature. The authors concluded that logistic regressions suggested that having a chronic mental illness significantly increases the likelihood of both trying an e-cigarette and being an e-cigarette user.
Chadi *et al.* [210] 2019	Harm	The authors reported on the relationship between **e-cigarette and marijuana use and depressive symptoms and suicidality** in a large sample of high school students. *Comparative groups* E-cigarettes themselves (current user, ≥ 1 per day for 30 days) Themselves (current marijuana user, ≥ 1 per day for 30 days) Dual users (e-cigarette and marijuana use, ≥ 1 per day for 30 days)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		Non-nicotine product user The authors stated that adolescents who admitted e-cigarette-only use, marijuana-only use, or dual e-cigarette and marijuana use had poorer mental health outcomes compared to those who denied use, when adjusting for demographic factors, use of other substances, and other relevant confounders. The association between depression and use of e-cigarettes has previously been reported in a nationally representative sample of adolescents, but the association between e-cigarette use and suicidality has not. The authors observed an increased likelihood of depressive symptoms and suicidal ideation in all three investigated substance use categories (e-cigarette-only, marijuana-only, and dual e-cigarette/marijuana use).
Kim[212] 2019	Harm	The author investigated the association between the use of **e-cigarettes and suicidal behaviours** in adolescents. *Comparative groups* E-cigarettes themselves (current users) Conventional combustible tobacco cigarette users (ever users) Non-e-cigarette users in past 30 days The author concluded that suicidal behaviours are significantly higher among current adolescent e-cigarette users than adolescents who have not used an e-cigarette in the past 30 days.
Lee *et al.* [213] 2019	Harm	The authors reported on the association of **depression and suicidality with electronic and conventional combustible tobacco cigarette use** in South Korean adolescents. *Comparative groups* E-cigarettes themselves (ever user) Conventional combustible tobacco cigarette users (ever user) Dual product users (e-cigarette and conventional combustible tobacco cigarette users) Never nicotine product users There were significant differences between tobacco cigarette and e-cigarette users: dual users had a higher prevalence of depression and suicidality for both lifetime and current use; e-cigarette-only users had higher levels of depression and suicidality than non-users; and female adolescents who were conventional-cigarette-only users, e-cigarette-only users, or dual users had a higher prevalence of depression and suicidality than male adolescents in those user categories. The authors concluded that the findings suggest an urgent need for evaluation of, and intervention in, e-cigarette use by health professionals providing smoking cessation programmes for adolescents.
Zvolensky *et al*[214] 2019	Harm	The authors reported on levels of **pain severity and anxiety sensitivity interplay among exclusive e-cigarette users and dual e-cigarette and conventional combustible tobacco cigarette users.** *Comparative groups* E-cigarettes themselves (daily users) Conventional combustible tobacco cigarette users (daily users) The authors concluded that the findings suggest that there needs to be further study of anxiety sensitivity and pain severity in the context of e-cigarette use, as there may be a benefit to screening for and clinically addressing these factors in order to help offset e-cigarette use.
		Body weight
Lanza *et al.* [215] 2017	Harm	The authors reported on the relationship **between e-cigarette and conventional combustible tobacco cigarette use and higher weight status (obesity).** *Comparative groups* E-cigarettes themselves (ever users) E-cigarettes themselves (current users) Conventional combustible tobacco cigarette users (current users) Conventional combustible tobacco cigarette users (ever users)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		Conventional combustible tobacco cigarette users (former users) The authors concluded that the relationship between obesity and cigarette smoking may extend to e-cigarette use among young adults.
Morean *et al.* [216] 2019	Harm	The authors reported on the relationship between **use of flavoured e-cigarettes and e-liquids with appetite control and weight loss.** *Comparative groups* E-cigarette users themselves (using ≥ 1 per day for 30 days, data on flavours) Conventional combustible tobacco cigarette users (current users ≥ 1 per day for 30 days) The authors concluded that a subset of adolescents reported using flavoured e-liquids for weight-related reasons. These adolescents reported vaping more frequently than their counterparts, raising concerns about increased nicotine exposure. Research is needed in order to understand where adolescents learn about weight-motivated vaping (e.g. friends, social media) and whether weight-related motives promote e-cigarette initiation among e-cigarette-naive individuals or continued/escalating use among current users.
		Sleep pattern
Boddu *et al.* [217] 2019	Harm	The authors reported on the **effects of e-cigarettes on sleep.** *Comparative groups* E-cigarettes users themselves Conventional combustible tobacco cigarette users Dual users (e-cigarettes and Conventional combustible tobacco cigarette users) The authors found that dual use of e-cigarettes with conventional tobacco has the highest risk for causing sleep disruption. They concluded that mechanistically, this finding is logical if nicotine is the causal agent of sleep disruption, as dual users are more likely to consume greater concentrations of nicotine than either smokers or vapers. This notion may reveal the underlying mechanism for poorer sleep quality and for increased odds and severity of cough in dual users.
Brett *et al.* [218] 2019	Harm	The authors reported on the relationship between **e-cigarette use and sleep health** in young adults. *Comparative groups* E-cigarettes users themselves (daily) E-cigarettes users themselves (not daily but at least monthly) Conventional combustible tobacco cigarette users (daily or weekly) The authors concluded that current combustible and e-cigarette users reported significantly more sleep difficulties than never users. E-cigarette users reported greater use of sleep medication than combustible cigarette users.
Riehm *et al.* [219] 2019	Harm	The authors reported on the relationship between **e-cigarette use and sleep-related complaints.** *Comparative groups* E-cigarettes users themselves (past year) E-cigarettes users themselves (ever use) Conventional combustible tobacco cigarette users (past year) Conventional combustible tobacco cigarette users (ever use) Dual product users (e-cigarette and conventional combustible tobacco cigarette users in past year) Non nicotine product users (in past year) The authors concluded that e-cigarette and dual-product use are significantly associated with greater odds of reporting sleep-related complaints among adolescents.
		Perceived health
Lequy *et al.* [220] 2019	Harm	The authors reported on **perceived health** and its association **with current use of e-cigarettes** in current and former smokers. *Comparative groups* E-cigarettes users themselves (ever, disposable) E-cigarettes users themselves (ever, refillable)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
		Conventional combustible tobacco cigarette (ever users) Conventional combustible tobacco cigarette users (former users who quit smoking within the last three years) The authors concluded that the findings suggest that the unhealthier current and former smokers felt, the more they tended to currently use e-cigarettes.

4.3.1.2.2 Cardiovascular diseases: cross-sectional surveys

Five cross-sectional survey papers reported on the relationship between e-cigarettes and myocardial infarction, other cardiovascular diseases, and the inflammatory signalling network underlying acute cardiac ischaemia (known as the splenocardiac axis).

The five cross-sectional survey papers reported mixed findings with respect to the association between e-cigarettes and cardiovascular diseases (Table 33).

One paper concluded that the findings indicated activation of the splenocardiac axis in a graded manner, from lowest in non-users, healthy control subjects, to mid-level in habitual e-cigarette users, to highest in tobacco cigarette smokers.[221]

One paper determined that e-cigarette use was independently associated with increased odds of having had a myocardial infarction, as was daily conventional cigarette smoking,[222] whereas another paper concluded that the pooled analysis of the 2016 and 2017 National Health Interview Survey found no association between e-cigarette use and a self-reported recent medical diagnosis of myocardial infarction or coronary heart disease.[223]

One paper reported that the SF-12 general health score, measuring 19 cardiopulmonary symptoms, was lower (worse) in e-cigarette users compared to non-users. E-cigarette users reported higher breathing difficulty scores, and greater proportions reported chest pain, palpitations, coronary heart disease, arrhythmia, chronic obstructive pulmonary disease, and asthma than non-users.[224]

A large study reported that 10% of 449,092 participants had cardiovascular disease.[225] The authors reported that dual use of e-cigarettes combined with conventional tobacco cigarettes was associated with significantly higher odds of cardiovascular disease compared with smoking tobacco cigarettes alone. They also found a graded increase in odds of cardiovascular disease with increasing frequency of e-cigarette exposure among current tobacco cigarette smokers. There was no significant association between e-cigarette-only use and cardiovascular disease among never tobacco cigarette smokers.

Table 33 Cross-sectional survey papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on cardiovascular diseases
Boas *et al.* [221] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **electronic and tobacco cigarettes** and the inflammatory signalling network underlying **acute cardiac ischaemia** (the Splenocardiac Axis). *Comparative groups* E-cigarettes users themselves (e-cigarettes for a minimum of 1 year) Conventional combustible tobacco cigarette users (for a minimum of 1 year) Healthy controls The authors reported that both hematopoietic tissue metabolic activity and aortic wall metabolic activity are increased in tobacco and e-cigarette users, and that plasma cotinine, an estimate of tobacco cigarette and e-cigarette burden, was weakly correlated with bone marrow activity. The authors concluded that the findings indicated activation of the Splenocardiac Axis in a graded manner, from non-user, healthy control subjects, to habitual e-cigarette users, to tobacco cigarette smokers
Alzahrani *et al.* [222] 2018	Harm	The authors reported on the relationship between **e-cigarette use and myocardial infarction.** *Comparative groups* E-cigarettes users themselves (daily) E-cigarettes users themselves (some days) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (daily) Conventional combustible tobacco cigarette users (some days) Conventional combustible tobacco cigarette users (former) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette) The authors concluded that e-cigarette use was independently associated with increased odds of having had a myocardial infarction.
Wang *et al.* [224] 2018	Harm	The authors reported on the relationship between **cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms**. *Comparative groups* E-cigarettes users themselves (current users) Conventional combustible tobacco cigarette users (ever) Dual users (e-cigarette and conventional combustible tobacco cigarette users) The SF-12 general health score, measuring 19 cardiopulmonary symptoms, was lower (worse) in dual users compared to cigarette-only users; this was specifically observed in the outcomes of breathing difficulties and a history of arrhythmia. E-cigarette-only use, compared to no product use, was associated with lower general health scores, higher breathing difficulty scores (typically and in the past month), and greater proportions of those who responded 'yes' to having chest pain, palpitations, coronary heart disease, arrhythmia, chronic obstructive pulmonary disease, and asthma. The authors suggested that the use of e-cigarettes alone may have contributed to cardiopulmonary health risks, particularly respiratory health risks.
Farsalinos *et al.* [223] 2019	Unable to determine	The authors reported on the relationship between **e-cigarette use, coronary heart disease, and myocardial infarction.** *Comparative groups* E-cigarettes users themselves (daily) E-cigarettes users themselves (some days) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (daily) Conventional combustible tobacco cigarette users (some days) Conventional combustible tobacco cigarette users (former users who stopped between 6 and 10 years) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on cardiovascular diseases
		The authors concluded that the pooled analysis of the 2016 and 2017 National Health Interview Survey showed no association between e-cigarette use and myocardial infarction or coronary heart disease. The associations between established risk factors, including smoking, and both conditions were remarkably consistent. The inconsistent associations observed in single-year surveys and the cross-sectional design of the National Health Interview Survey cannot substantiate any link between e-cigarette use and an elevated risk for myocardial infarction or coronary heart disease.
Osei *et al.* [225] 2019a	Harm	The authors reported on the association between **e-cigarette use and cardiovascular disease**. *Comparative groups* E-cigarettes users themselves (ever use) E-cigarettes users themselves (daily) E-cigarettes users themselves (occasional) Conventional combustible tobacco cigarette users (current users) Conventional combustible tobacco cigarette users (ever) Dual users (e-cigarette and conventional combustible tobacco cigarette users) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette) The authors concluded that their results suggest significantly higher odds of cardiovascular disease among dual users of e-cigarettes and combustible cigarettes compared with combustible tobacco cigarette-only users. They also queried whether the current lack of significant association between e-cigarette use and cardiovascular disease among never combustible cigarette smokers may be due to the younger age of this group.

4.3.1.2.3 Cancers: cross-sectional surveys

Five cross-sectional survey papers reported on the relationship between e-cigarettes and a range of cancer-related risk markers and outcomes (Table 34). These included measuring the total nicotine equivalents or dose, and the nicotine metabolite ratio. A number of tobacco-specific smoking-related carcinogens are measured in the cross-sectional papers, namely: N'-Nitrosonornicotine (NNN), which is a risk marker for oral and oesophageal cancer; and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides, which are risk markers for lung cancer. Oral cavity cancer was assessed in the cross-sectional papers by cytologic examination of micronuclei in the oral mucosa. Salivary specimens were assayed for cotinine (a biomarker of nicotine exposure), and urine specimens for NNAL (a biomarker of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)).

Two of the five cross-sectional survey papers examined levels of tobacco-related carcinogens. The authors of one cross-sectional survey reported on the relationship between smokers of combustible cigarettes only, former smokers with long-term e-cigarette-only use, former smokers with long-term NRT-only use, long-term dual users of both combustible cigarettes and e-cigarettes, and long-term users of both combustible cigarettes and NRT with exposure to nicotine, tobacco-related carcinogens, and toxins.[226] The authors concluded that e-cigarette-only users had significantly lower 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol levels levels (which is a risk marker for lung cancer) than all other groups. Combustible cigarette-only users, dual combustible cigarette and NRT users, and dual combustible cigarette and e-cigarette users had largely similar levels of tobacco specific N-nitrosamines (most of which are carcinogenic) and volatile organic compounds (which are also carcinogenic). The second cross-sectional survey paper examined the relationship between smokeless tobacco and nicotine and carcinogen exposures.[227] The authors concluded that adolescents who used smokeless tobacco products were exposed to substantial levels of nicotine and a specific carcinogen (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNK); However, this paper indicated that exclusive e-cigarette users have non-detectable concentrations of salivary nicotine and very low concentrations of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol compared with smoking or smokeless. Although exposed to lower levels than adult smokeless tobacco product users, the findings are concerning,

given the young age of the sample and the tendency for smokeless tobacco users to increase use intensity over time.

Two survey papers measured markers for oral cancer or oesophageal cancer. One study reported that the highest prevalence of micronuclei (indicative elements of genomic instability which may have a clinical application in screening tests for risk categories of oral cavity carcinoma) was observed in smokers, followed by e-cigarette users, and then by non-users, who had the lowest prevalence of micronuclei among the three groups.[228] One study reported that N'-nitrosonornicotine (marker for oral and oesophageal cancer) is formed endogenously by e-cigarette users, and exposure to it in e-cigarette users' saliva is lower than in smokers. [229]

Table 34 Cross-sectional survey papers on cancers, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on cancers
Franco *et al.* [228] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **e-cigarettes and micronuclei prevalence indicative of oral cavity cancer** following cytologic examination of oral mucosa. *Comparative groups* E-cigarettes users themselves (current for ≥ 6 months) Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Never smokers (conventional combustible tobacco cigarette) A higher prevalence of micronuclei was observed in smokers relative to e-cigarette smokers, and non-users had the lowest prevalence of micronuclei among the three groups. The authors stated that micronuclei are indicative elements of genomic instability and may have a clinical application in screening tests for risk categories of oral cavity carcinoma. They also suggested that e-cigarettes seem to be safe for oral cells and should be suggested as an aid for smoking cessation.
Shahab *et al.* [226] 2017	Less harmful than conventional combustible tobacco cigarettes for one indicator	The authors reported on the relationship between smokers of **combustible cigarettes** only, former smokers with long-term **e-cigarette-only** use, former smokers with long-term NRT-only use, long-term dual users of both combustible cigarettes and e-cigarettes, and long-term users of both combustible cigarettes and NRT with **exposure to nicotine, tobacco-related carcinogens, and toxins**. *Comparative groups* E-cigarettes users themselves (former conventional combustible tobacco cigarette users) Conventional combustible tobacco cigarette users (users) Conventional combustible tobacco cigarette users (former users on nicotine replacement therapy) Dual users (e-cigarettes and conventional combustible tobacco cigarettes) Dual users (conventional combustible tobacco cigarettes and nicotine replacement therapy) Across the five groups (n=36–37 per group), nicotine, carcinogen, and toxin exposures were assessed using urine and saliva samples, which were analysed for biomarkers of nicotine, tobacco-specific N-nitrosamines (TSNAs), and volatile organic compounds. The authors concluded that e-cigarette-only users had significantly lower 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels than all other groups. Combustible cigarette-only users, dual combustible cigarette and nicotine replacement therapy (NRT) users, and dual combustible cigarette and e-cigarette users had largely similar levels of tobacco-specific N-nitrosamines and volatile organic compounds metabolites.
Bustamante *et al.* [229] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **e-cigarette** use and the presence of N'-nitrosonornicotine (NNN) as a **risk marker of oral and oesophageal cancer.** *Comparative groups* E-cigarettes users themselves only (daily for 3 months) Conventional combustible tobacco cigarette users only (smoked ≥ 10 per day for 6 months)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on cancers
		Never smokers (conventional combustible tobacco cigarette) The authors concluded that N'-nitrosonornicotine is formed endogenously in e-cigarette users, and while overall exposure to N'-nitrosonornicotine in e-cigarette users is lower than in smokers, the known carcinogenic potency of N'-nitrosonornicotine should be monitored (specifically salivary rather than urinary NNN) in order to assess the potential relationship of e-cigarettes with oral and oesophageal cancers
Carroll *et al.* [230] 2018	Harm	The authors reported on the relationship of **cigarette smokers and electronic nicotine delivery system (ENDS) users with nicotine metabolism and nicotine and carcinogen exposure.** *Comparative groups* E-cigarettes users themselves only (daily for three months) Conventional combustible tobacco cigarette users (exclusive, ≥ 5 per day for 3 months) Dual users (not specified) Among smokers, there were inverse relationships between nicotine metabolite ratio and total nicotine equivalents (r=-0.45) and between nicotine metabolism nicotine metabolite ratio and (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides [NNAL] (r=-0.50). Among dual users, nicotine metabolism, nicotine metabolite ratio and total nicotine equivalents, and nicotine metabolite ratio and (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides were not associated. Among ENDS users, nicotine metabolism, nicotine metabolite ratio and total nicotine equivalents were not associated.
Chaffee *et al.* [227] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors assessed tobacco product use (smokeless, combustible, and electronic cigarettes) and nicotine and carcinogen exposures**.** *Comparative groups* E-cigarettes users themselves (last seven days) Conventional combustible tobacco cigarette users (last 7 days) E-cigarettes users themselves only Conventional combustible tobacco cigarette users only Smokeless tobacco users only Dual users (e-cigarettes and conventional combustible tobacco) Dual users (smokeless and conventional combustible tobacco) Poly users (e-cigarettes together with smokeless and/or combustible tobacco) The authors concluded that adolescents who use **smokeless tobacco products (including e-cigarettes)** are exposed to substantial levels of nicotine and to the biomarker of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Although exposed to lower levels than adult smokeless tobacco product users, the findings are concerning given the young age of the sample and the tendency for smokeless tobacco product users to increase use intensity over time. However, the conclusion appears to be based on smokeless tobacco users of whom some were smokers, and some were e-cigarette users, so it is impossible to isolate the effect of e-cigarette use in this group. In addition, Table 2 of Chaffee *et al.'s* paper indicates that exclusive e-cigarette users have non-detectable concentrations of salivary nicotine and very low concentrations of NNAL compared with smoking or smokeless.

4.3.1.2.4 Respiratory diseases: cross-sectional surveys

Twenty-one cross-sectional survey papers reported on the relationship between e-cigarettes and respiratory diseases (Table 35). The papers examined e-cigarettes and their effect on respiratory function, their association with signs and symptoms of respiratory diseases, their association with subjective symptoms of ill health, and their association with diagnosed respiratory diseases.

The measures of respiratory function included: lung capacity, volume of air expired in a normal breath or a forced breath, and ratios between lung capacity and respiratory expiration. These were measured using spirometry. Spirometry measures included: forced vital capacity (FVC), forced

expiratory volume in the first second (FEV1), forced expiratory ratio (FEV1/FVC), and peak expiratory flow (PEF). A lower percentage forced expiratory flow is an indicator of lower lung function.

The signs and symptoms of possible respiratory diseases assessed in e-cigarette users in the surveys included: dry or irritated mouth, dry or irritated throat, cough (dry or productive), sputum production, and wheezing or whistling. The subjective symptoms of ill health as a result of e-cigarette use assessed in the survey papers included: nose irritation (itchy nose, uncomfortable smell, and sneezing), eye irritation (watery eye, sore eye, and reddish eye), and throat irritation (sore throat, dry throat, cough, and choking sensation).

The measures of propensity for respiratory diseases among e-cigarette users included assessment of immune gene expression profiles and lung function.

One study reported that e-cigarette users had several negative changes in the content and consistency of their sputum.[231] E-cigarette users exhibited significant increases in aldehyde detoxification and oxidative stress-related proteins in their sputum, normally observed in higher levels in conventional cigarette smokers than in non-smokers. The levels of innate defence proteins in sputum associated with chronic obstructive pulmonary disease, such as elastase and matrix metalloproteinase-9, were significantly elevated in e-cigarette users as well. E-cigarette users' sputum also uniquely exhibited significant increases in neutrophil granulocyte-related and neutrophil extracellular trap-related proteins. Peripheral neutrophils from e-cigarette users showed increased susceptibility to phorbol 12-myristate 13-acetate-induced neutrophil extracellular traposis. Finally, a compositional change in the gel-forming building blocks of airway mucus (i.e. an elevated concentration of one mucin) was observed in both conventional cigarette smokers and e-cigarette users.

One paper concluded that fractional exhaled nitric oxide (FeNO) was decreased in e-cigarette users, but the decrease was not statistically significant.[232] Also, the use of e-cigarettes significantly impaired various lung function parameters, and the pattern of impairment exhibited a peripheral obstructive airway involvement.

Six other papers reported respiratory symptoms in e-cigarette users. The first paper noted a strong association between respiratory symptoms (cough or phlegm) in adolescent e-cigarette users.[233] The second paper determined that, after controlling for covariates, respiratory symptoms (such as cough, sputum production, or wheeze) were significantly associated with adult dual use, tobacco cigarette smoking only, and former tobacco smoking, but not with former vaping or e-cigarette use when compared to non-users (non-smokers and non-vapers).[234] The third paper reported that self-reported health complaints among 20 adults who were mainly dual users mostly consisted of upper airway irritation with acute effect. [235] The fourth paper concluded that most e-cigarette users reported at least one symptom, most commonly a cough or a dry or irritated mouth or throat.[236] The fifth paper reported that e-cigarette use was associated with increased risk of wheezing and related respiratory symptoms.[237] The sixth paper concluded that adolescent e-cigarette users had increased rates of chronic bronchitic symptoms.[238]

Seven papers reported a harmful association between e-cigarette use and asthma in adolescents, adults, and passive vapers. One paper concluded that e-cigarette use by adolescents was independently associated with an asthma diagnosis.[239] Another paper concluded that recent e-cigarette use by adolescents with asthma was associated with having an asthma attack in the 12 months prior to the survey.[240] The third paper reported that e-cigarette use had an increased association with asthma and that users were more likely to have had days absent from school due to severe asthma symptoms.[241] The fourth paper found that active and passive vaping among adolescents was significantly associated with the onset of asthma symptoms.[242] The fifth paper reported that adult asthmatic patients who continue to smoke conventional tobacco cigarettes or replace them with e-cigarettes have a significant decline in their pulmonary function and their asthma control test score in comparison with non-user asthmatic patients.[243] The remaining two papers concluded that e-cigarette use may be associated with asthma among never-smokers.[244] [245]

One study found a significant independent association between e-cigarette use and chronic respiratory disorders (asthma and chronic obstructive pulmonary disease) compared to non-use.[246]

One study described an epidemiologic investigation into reports of several cases of lung injury in previously healthy persons in Illinois who reported e-cigarette use.[247] Overall, 75 (87%) of 86 interviewed patients reported using e-cigarette products containing tetrahydrocannabinol, and 61 (71%) reported using nicotine-containing products. Nearly all (96%) tetrahydrocannabinol-containing products reported were packaged, prefilled cartridges, and 89% were acquired from informal sourcesOne paper reported that all genes displaying decreased expression in cigarette smokers (n=53) were also displaying decreased expression in e-cigarette smokers.[248] Additionally, vaping e-cigarettes was associated with suppression of many unique genes (n=305). Furthermore, the e-cigarette users showed a greater suppression of genes commonly changed in cigarette smokers.

One paper found that non-smokers who are passively exposed to e-cigarettes absorb nicotine.[249]

One paper concluded that the effects of e-cigarettes on voice, using subjective and objective voice analysis, were mild compared with conventional tobacco cigarettes. [250]

Table 35 Cross-sectional survey papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		Respiratory symptoms
Wang *et al.* [233] 2016	Harm	The authors reported on the relationship between **e-cigarette use and respiratory symptoms**. *Comparative groups* E-cigarettes users themselves (current users) Conventional combustible tobacco cigarette users (experimental) Conventional combustible tobacco cigarette users (current users) Conventional combustible tobacco cigarette users (former users) Never smokers (conventional combustible tobacco cigarette) The authors noted that the strong association of respiratory symptoms (cough or phlegm for 3 consecutive months in the past 12 months) in adolescent e-cigarette users who never smoked tobacco cigarettes (AOR: 2.06; 95% CI: 1.24–3.42) is comparable with that found in adolescent occasional smokers (AOR: 1.72; 95% CI: 1.01–2.93) in other Hong Kong study populations.
McConnell *et al.* [238] 2017	Harm	The authors reported on the relationship of **e-cigarette use with chronic bronchitis symptoms and wheeze** in an adolescent population. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (former users) Conventional combustible tobacco cigarette users (current) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette) Never users (cigar) Never users (pipe) Never users (hookah) Former users (cigar) Former users (pipe) Former users (hookah users) The authors concluded that adolescent e-cigarette users had increased rates of chronic bronchitic symptoms.
Hedman *et al.* [234] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the association of **e-cigarette use** with smoking habits, demographic factors, and **respiratory symptoms** (such as sputum production, chronic productive cough, and wheeze). *Comparative groups* E-cigarettes users themselves (daily) E-cigarettes users themselves (sometimes) Conventional combustible tobacco cigarette users (current users) Conventional combustible tobacco cigarette users (former users) Dual users (e-cigarette and combustible tobacco cigarette) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		Respiratory symptoms (long-standing cough, sputum production, chronic productive cough, any wheeze, recurrent wheeze, any respiratory symptoms) were most common among dual users of conventional combustible tobacco cigarettes and e-cigarettes, and among former smokers and non-smokers who used e-cigarettes. In a regression analysis adjusted for sex, age group, survey, and educational level, having any respiratory symptoms was significantly associated with dual use (OR: 4.03; 95% CI: 3.23–5.02), smoking only (OR: 2.55; 95% CI: 2.36–2.77), and former smoking without e-cigarette use (OR: 1.27; 95% CI: 1.19–1.36), while former smoking with e-cigarette use (OR: 1.47; 95% CI: 0.91–2.37) and non-smoking with e-cigarette use (OR: 1.46; 95% CI: 0.93–2.29) did not reach statistical significance. Non-smokers without e-cigarette use were used as the reference in the regression analysis.
Lestari *et al.* [235] 2018	Harm	The authors reported on the relationship between **e-cigarette use**, a range of **subjective feelings of upper respiratory well-being,** and **formaldehyde vapour concentration**. *Comparative groups* E-cigarettes users themselves (daily and number per day) The authors concluded that health complaints were mostly upper airway irritation with acute effect, and that cotinine in urine was mostly positive.
Reidel *et al.* [231] 2018	Harm	The authors reported on the relationship between cigarette smokers, **e-cigarette** users, and non-smokers **with the profile of innate defence proteins** in airway secretions of mucins MUC5AC and MUC5B, and of neutrophil extracellular trap formation rates. *Comparative groups* E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current) Never smokers (conventional combustible tobacco cigarette) The authors concluded that e-cigarette use alters the profile of innate defence proteins in airway secretions, inducing similar and unique changes relative to cigarette smoking. These data challenge the concept that e-cigarettes are a healthier alternative to cigarettes.
Tuhanioglu *et al.* [250] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the effects of **e-cigarettes on voice performance** compared with conventional combustible tobacco cigarettes. *Comparative groups* E-cigarettes users themselves (between 1 and 3years) Conventional combustible tobacco cigarette users (daily 10 to 20 cigarettes for 1 to 5 years) Never smokers (conventional combustible tobacco cigarette) The authors concluded that the effects of e-cigarettes on voice were detected as mild compared with those of conventional combustible tobacco cigarettes, according to the subjective and objective voice analysis results in the study.
King *et al.* [236] 2019	Harm	The authors reported on the **adverse symptoms identified in e-cigarette** users. *Comparative groups* E-cigarettes users themselves (ever and current) E-cigarettes users themselves (former users) Conventional combustible tobacco cigarette users (daily or some days) Conventional combustible tobacco cigarette users (former) Never smokers (conventional combustible tobacco cigarette) The authors concluded that most e-cigarette users reported at least one symptom, most commonly a cough or a dry or irritated mouth or throat. Former cigarette smokers who used e-cigarettes in the past 30 days were less likely than current or never-smokers to report adverse symptoms of e-cigarette use.
Li *et al.* [237] 2019	Harm	The authors reported on the association between smokers, dual users, and **vapers with wheezing and related respiratory symptoms**. *Comparative groups*

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		E-cigarettes users themselves (exclusive) E-cigarettes users themselves (ever and current) Conventional combustible tobacco cigarette users (exclusive users) Conventional combustible tobacco cigarette users (ever and current) Dual users (e-cigarette and combustible tobacco cigarette) The authors concluded that vaping was associated with increased risk of wheezing and related respiratory symptoms. Current vapers had a lower risk of wheezing and related respiratory symptoms than current smokers or dual users, but a higher risk than non-users. Both dual use and smoking significantly increased the risk of wheezing and related respiratory symptoms.
Meo *et al.* [232] 2019	Less harmful than conventional combustible tobacco cigarettes Harm	The authors reported on the impact of **e-cigarettes on lung function** and **fractional exhaled nitric oxide** (FeNO) among 60 young healthy male adults. *Comparative groups* E-cigarettes users themselves (daily in past 6 months) Non-users (conventional tobacco cigarettes, shisha) Non-users (e-cigarettes) The authors concluded that fractional exhaled nitric oxide was decreased in e-cigarette users, but it did not reach the level of significance. Also, the use of e-cigarettes significantly impaired various lung function parameters, and the pattern of impairment exhibited a peripheral obstructive airway involvement.
		Asthma
Cho *et al.* [241] 2016	Harm	The authors reported on findings regarding the association between **e-cigarette use and asthma** (students' self-reported doctor diagnosis in past 12 months). *Comparative groups* E-cigarettes users themselves (ever and current) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (ever and current) Conventional combustible tobacco cigarette users (former) Never users (conventional combustible tobacco cigarette) The authors concluded that e-cigarette users have an increased association with asthma and are more likely to have had days absent from school due to severe asthma symptoms than non-users.
Choi *et al.* [240] 2016	Harm	The authors reported findings on the association between **e-cigarette use and asthma**. *Comparative groups* E-cigarettes users themselves (ever) E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current users grouped by number of days used) The authors concluded that e-cigarette use is more common among Florida high school youth with asthma and is associated with susceptibility to cigarette smoking.
Kim *et al.* [242] 2017	Harm	The authors reported on the association of **active and passive e-cigarette vaping with asthma**. *Comparative groups* E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current) Passive smokers The authors concluded that the study demonstrated a positive association between e-cigarette use and an asthmatic episode in the past 12 months, and that this association was observed when adjustments for active and passive vaping exposure were included in the analysis. However, e-cigarette vaping in the past month was not significantly associated with lifetime asthma after adjusting for active and passive vaping. Active and passive vaping were thus considered to be more influential on previous

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		asthma history than recent e-cigarette vaping. As a high proportion of e-cigarette smokers are generally previous active smokers, the effects of previous active vaping were high in this group.
Schweitzer *et al.* [239] 2017	Harm	The authors reported on the association of **e-cigarettes with asthma**, controlling for cigarette smoking, marijuana use, and six demographic covariates. *Comparative groups* E-cigarettes users themselves (ever) E-cigarettes users themselves (current and data on device) Conventional combustible tobacco cigarette users (ever users) Conventional combustible tobacco cigarette users (current) Never smokers (conventional combustible tobacco cigarette) Current e-cigarette use was associated with currently having (versus never having) asthma (AOR: 1.48; CI: 1.26–1.74) and with previously having (versus never having) asthma (AOR: 1.22; CI: 1.07–1.40). The level of confidence for CI is not reported in paper. The authors concluded that e-cigarette use by adolescents is independently associated with asthma.
AboElNaga[243] 2018	Harm	The author reported on the relationship between **e-cigarettes and specific respiratory outcomes**, including asthma control test, lung function, blood eosinophils, and airway immunoinflammatory phenotype. *Comparative groups* Conventional combustible tobacco cigarette users (ever and current) E-cigarettes users themselves (current) Dual users (e-cigarette and conventional combustible tobacco cigarette in past 12 months) Non-smokers (conventional combustible tobacco cigarette) The asthmatic patients were reported to have significant differences in spirometry and distribution of sputum cell subtypes between non-smokers, current conventional combustible tobacco cigarette smokers, and e-cigarette users. The author stated that asthmatic smoker patients who smoke e-cigarettes develop mixed sputum subtype; there was no difference in the pulmonary function or asthma control of patients who smoke e-cigarettes compared with that observed in conventional smokers. The author concluded that asthmatic patients who continue to smoke conventional combustible tobacco cigarettes or replace them with e-cigarettes have a significant decline in their pulmonary function, as recorded by spirometry parameters (FVC, FEV1, FEV1/FVC, maximal mid expiratory flow, and peak expiratory flow rate), and asthma control test score, in comparison with non-smoking asthmatic patients.
Osei *et al.* [244] 2019b	Harm	The authors reported on the relationship between **e-cigarette use and asthma** among never combustible cigarette smokers. *Comparative groups* E-cigarettes users themselves (ever) E-cigarettes users themselves (daily) E-cigarettes users themselves (occasional) Conventional combustible tobacco cigarette users (ever) Conventional combustible tobacco cigarette users (current) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette) Dual user (e-cigarettes and combustible tobacco cigarettes) The authors concluded that there was an increased rate of asthma among never combustible cigarette smoker e-cigarette users, with 39% higher odds of self-reported asthma compared to never e-cigarette users (OR: 1.39; 95% CI: 1.15–1.68).
Perez *et al.* [245] 2019	Harm	The authors reported on the association of **e-cigarette use and asthma** in never- smokers. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (former) Never smokers (conventional combustible tobacco cigarette)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		Never vapers (e-cigarette) Dual users (e-cigarettes and conventional combustible tobacco for ≥ 6 months) The authors concluded that e-cigarette use may be associated with asthma among never-smokers.
		Other respiratory conditions
Martin *et al.* [248] 2016	Harm	The authors reported on the relationship between non-smokers, cigarette smokers, and **e-cigarette users** and **immune gene expression profiles** assessed from nasal scrape biopsies, nasal lavage, urine, and serum. *Comparative groups* E-cigarettes users themselves (current for ≥ 6 months) E-cigarettes users who were former smokers (current for ≥ 6 months) Conventional combustible tobacco cigarette users Non-smokers (conventional combustible tobacco cigarette) The authors concluded that the data indicate that vaping e-cigarettes is associated with decreased expression of a large number of immune-related genes, which are consistent with immune suppression at the level of the nasal mucosal.
Wills *et al.* [246] 2019	Harm	The authors reported on the association of **e-cigarette use with diagnosed respiratory disorders**. *Comparative groups* E-cigarettes users themselves (ever) Conventional combustible tobacco cigarette users (ever and current) Non-smokers (conventional combustible tobacco cigarette) The authors concluded that the study showed a significant independent association between e-cigarette use and chronic respiratory disorders. The association was stronger among non-smokers than among smokers.
		Lung injury
Ghinai *et al.* [247] 2019	Harm	In July 2019, the Illinois Department of Public Health and the Wisconsin Department of Health Services launched a coordinated epidemiologic investigation after receiving **reports of several cases of lung injury** in previously healthy persons who reported using e-cigarettes or vaping. *Comparative groups* Tetrahydrocannabinol (THC) containing e-cigarette products users (exclusive) Nicotine containing products users (exclusive) Dual or poly user (tetrahydrocannabinol (THC) containing e-cigarette products and other nicotine products users) Dank vapes tetrahydrocannabinol (THC) containing products users (exclusive) The Centers for Disease Control and Prevention reported the precise source of the outbreak as currently unknown; however, the predominant use of prefilled tetrahydrocannabinol-containing cartridges among patients with lung injury associated with e-cigarette use suggested that these products played an important role.
		Passive smoking
Bayly *et al.* [249] 2019	Harm	The authors reported on the relationship between second-hand **e-cigarette aerosol exposure and asthma exacerbations** among youth with asthma. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Never smokers (conventional combustible tobacco cigarette) Never vapers (e-cigarette) Never users (cigar) Never users (hookah) Passive e-cigarette exposure (current) Cigar users (current) Cigar users (former)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on respiratory diseases
		Hookah users (current) Hookah users (former) The results found that airborne markers were statistically higher in the homes of conventional combustible tobacco cigarette smokers (5.7 times higher) than in the homes of e-cigarette users. However, concentrations of both biomarkers among non-smokers exposed to conventional combustible tobacco cigarettes and to e-cigarette vapour were statistically similar (2 and 1.4 times higher, respectively). The authors concluded that non-smokers passively exposed to e-cigarettes absorb nicotine.
Tackett *et al.*[251] 2019	Neither harm or benefit	The authors reported on a preliminary exploration of **second-hand smoke or vapour exposure in youth with sickle cell disease** through biochemical verification of cotinine, pulmonary functioning, and healthcare utilisation. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (former) Conventional tobacco cigarettes users (current) Conventional tobacco cigarettes users (former) Never smokers (conventional tobacco cigarettes users) Never vapers (e-cigarette) The authors concluded that most of the youth (88%) were exposed to second-hand smoke via salivary cotinine. Interestingly, no significant associations were observed between youth cotinine levels and emergency department utilisation, physician-reported sickle cell crises, or pulmonary functioning. Present findings indicate a need to assess for second-hand smoke using objective assessment measures.

4.3.1.2.5 Oral diseases: cross-sectional surveys

The 14 cross-sectional survey papers grouped under the 'oral disease' heading reported on clinically, radiographically, laboratory, and self-reported measures of oral health (Table 36). These included the clinical and radiographic peri-implant parameters that assess: cavities, gum disease, dental stains, extent of full-mouth and peri-implant plaque, and bleeding on probing. Probing depth was measured at different sites in each tooth, including maxillary and mandibular teeth. Peri-implant bone loss and marginal bone loss were measured. Levels of tumour necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), interleukin -1 beta, and matrix metalloproteinase-9 in peri-implant sulcular fluid were ascertained. Levels of immunoglobulin A (IgA), lysozyme, and lactoferrin levels in unstimulated saliva were also measured. Some papers measured outcomes such as gingival pain and/or bleeding, tongue and/or inside-cheek pain, cracked or broken teeth, number of permanent teeth removed due to non-traumatic causes, and unstimulated whole salivary flow rate. One paper determined carrier status for oral Candida in survey participants.

There were 11 studies on oral health; 9 reported that there was a harmful association between e-cigarettes and oral health and 2 reported that e-cigarettes were less harmful than conventional tobacco cigarettes for oral health.

One study reported that daily e-cigarette use among adolescents may be a risk factor for cracked or broken teeth and for tongue and/or inside-cheek pain.[252] Seven studies concluded that periodontal inflammation and/or disease were poor among e-cigarette users when compared to non-users.[253-255 256 256-258] One study found that daily e-cigarette use was independently associated with 78% higher odds of permanent tooth extraction due to caries.[259] Another study determined that use of conventional tobacco cigarettes and dual use of e-cigarettes and tobacco cigarettes were associated with adolescents self-reporting past-year diagnosis of dental problems.

On the other hand, two studies reported that clinical and radiographic parameters of periodontal inflammation were poorer in tobacco cigarette users than in e-cigarette users and in never-smokers.[260 261] The papers' abstracts implied that e-cigarette users and never-smokers have similar levels of oral health.

There were three papers on markers for oral infection in e-cigarette users. One paper examined the relationship of e-cigarettes with selected antibacterial properties of saliva (IgA, lysozyme, and lactoferrin levels) and concluded that the saliva of e-cigarette users showed negative changes in antibacterial properties compared with non-users and with tobacco cigarette smokers.[262] Another paper reported that oral *Candida albicans* carriage was significantly higher among tobacco cigarette smokers, water pipe smokers, and e-cigarette users than among non-users.[263] On the other hand, the third paper reported that people who regularly use e-cigarettes do not have measurably different oral or gut bacterial communities compared to non-smokers.[264]

Table 36 Cross-sectional survey papers on oral diseases, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on oral diseases
		Oral health
Cho[252] 2017	Harm	The author reported on the relationship between **e-cigarette use and oral health**, measured as gingival pain and/or bleeding, tongue and/or inside-cheek pain, and cracked or broken teeth. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (daily, nicotine-free) E-cigarettes users themselves (daily, nicotine use) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (daily, nicotine free) Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Never smokers (conventional tobacco cigarettes users) Never vapers (e-cigarette) The author reported that former e-cigarette users had a significantly higher occurrence of cracked or broken teeth than never e-cigarette users, and that daily e-cigarette users had a significantly higher occurrence of tongue and/or inside-cheek pain than never e-cigarette users, concluding that daily e-cigarette use among adolescents may be a risk factor for cracked or broken teeth and for tongue and/or inside-cheek pain.
Javed *et al.* [253] 2017	Harm	The authors reported on the relationship between cigarette smokers (group 1), individuals exclusively **vaping e-cigarettes** (group 2), and never-smokers (group 3) with **periodontal parameters and self-perceived oral symptoms**. *Comparative groups* E-cigarettes users themselves who were never smokers (exclusive for ≥ 12 months, group 2) Conventional combustible tobacco cigarette users (≥ 5 daily for ≥ 12 months, group 1) Never users (any type of nicotine product, group 3) Plaque index (p<0.01) and probing depth ≥4 mm (p<0.01) were significantly higher in groups 1 and 2 than in group 3. Bleeding on probing was significantly higher in group 3 than in groups 1 and 2 (p<0.01). There was no difference in the number of missing teeth, clinical attachment loss, or marginal bone loss between all groups. Gingival pain was more often reported by individuals in group 1 than by individuals in groups 2 or 3 (p<0.01).
Akinkugbe *et al.* [254] 2018	Harm	The authors investigated associations between self-reported use of cigarettes and **e-cigarettes with oral health status.** *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (ever) Conventional combustible tobacco cigarette users (ever)) Conventional combustible tobacco cigarette users (current) Current dual users (e-cigarette and conventional combustible tobacco cigarette) Ever dual users (e-cigarette and conventional combustible tobacco cigarette) The authors used adjusted logistic regression to estimate prevalence odds ratios (PORs) and 95% CIs. Self-reported provider-diagnosed dental

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on oral diseases
		problems' covariate-adjusted values were: POR: 1.50 (95% CI: 1.18–1.90) in current cigarette users and POR: 1.11 (95% CI: 0.79–1.55) in current e-cigarette users. Ever use of cigarettes and e-cigarettes was likewise associated with increased prevalence odds of self-reported past-year diagnosis of dental problems, although to a lesser magnitude. The authors concluded that dual use of e-cigarettes and conventional combustible tobacco cigarettes is associated with poor oral health outcomes among adolescents.
Al-Aali *et al.* [255] 2018	Harm	The authors reported on the relationship between **vaping e-cigarettes and never smoking** with clinical and radiographic **peri-implant parameters** and levels of tumour necrosis factor alpha (TNF-alpha) and interleukin (IL)-1beta. *Comparative groups* E-cigarettes users themselves (using for ≥ 1 year) Never-smokers (conventional combustible tobacco cigarette) The authors concluded that clinical and radiographic peri-implant parameters were compromised among vaping individuals. The authors concluded that increased levels of proinflammatory cytokines in peri-implant sulcular fluid may suggest greater local inflammatory response in vaping individuals for peri-implant inflammation and peri-implant bone loss (p=0.016). A significant positive correlation was found between IL-1 beta and peri-implant bone loss (p=0.018) in e-cigarette users compared to non-users of e-cigarettes.
AlQahtani *et al.* [256] 2018	Harm	The authors reported on the relationship of water pipe smokers, **e-cigarette users**, and cigarette smokers with **peri-implant parameters and local levels of proinflammatory cytokines**; specifically, periodontal and peri-implant plaque index, bleeding on probing, and **probing depth** (≥4 mm) and **levels of TNF-alpha,** interleukin **-6**, and interleukin **-1 beta** in peri-implant sulcular fluid. *Comparative groups* E-cigarettes users themselves (current, ≥ 10 per day use for ≥ 5 years)) Conventional combustible tobacco cigarette users (current daily use) Non-smokers (conventional combustible tobacco cigarette) Water pipe users (current daily use) Mean peri-implant plaque index (p<0.05), probing depth ≥4 mm (p<0.05), and total radiographic bone loss (p<0.01) were significantly higher among cigarette smokers, water pipe smokers, and subjects using e-cigarettes compared with non-smokers. Statistical differences in bleeding on probing were observed in non-smokers (p<0.01) compared to cigarette smokers, water pipe smokers, and subjects using e-cigarettes. Cigarette smokers and water pipe smokers showed significantly higher probing depth ≥4 mm and radiographic bone loss compared with subjects using e-cigarettes (p<0.05). Levels of TNF-alpha, IL-6, and IL-1 beta were significantly higher in cigarette smokers, water pipe smokers, and subjects using e-cigarettes compared to non-smokers. There were no statistical differences in the mean levels of all proinflammatory cytokines among individuals who were cigarette smokers or water pipe smokers.
Mokeem *et al.* [260] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between cigarette smoking, water pipe smoking**, e-cigarette** using, and never smoking behaviours, and outcome **oral health measures** of clinical (plaque index, bleeding on probing, probing pocket depth, and clinical attachment loss), radiographic (marginal bone loss), and periodontal parameters, and of whole salivary cotinine, interleukin -1 beta, and interleukin -6 levels. *Comparative groups* E-cigarettes users themselves who never smoked (exclusive for ≥ 12 months) Conventional combustible tobacco cigarette users (daily for ≥ 12 months) Never smokers (conventional combustible tobacco cigarette) Water pipe users (current daily use for ≥ 12 months)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on oral diseases
		The authors reported that clinical and radiographic parameters of periodontal inflammation were poorer in cigarette and water pipe smokers than in e-cigarette users and never-smokers, and that whole salivary cotinine levels were similar in all groups. Whole salivary interleukin -1 beta and interleukin -6 levels were higher in cigarette and water pipe smokers than e-cigarette users and never-smokers.
Alqahtani *et al.* [265] 2019	Harm	The authors compared **cotinine levels** in the **peri-implant sulcular fluid** among cigarette and water pipe smokers, **e-cigarette users**, and non-smokers. *Comparative groups* E-cigarettes users themselves (daily for ≥ 1 year) Conventional combustible tobacco cigarette users (current, daily for ≥ 1 year) Never smokers (conventional combustible tobacco cigarette users) Other product users (waterpipe users) The authors concluded that habitual use of nicotinic products enhances the expression of cotinine in the peri-implant sulcular fluid. Cotinine levels in the peri-implant sulcular fluid of cigarette and water pipe smokers and e-cigarette users are comparable.
ArRejaie *et al.* [261] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between cigarette smokers', **e-cigarette vaping** individuals', and non-smokers' **peri-implant health** using clinical and radiographic peri-implant parameters (specifically peri-implant plaque index, bleeding on probing, probing depth, and marginal bone loss), levels of matrix metalloproteinase-9, and interleukin -1 beta levels. *Comparative groups* E-cigarettes users themselves (≥ 1 year) Conventional combustible tobacco cigarette users (smoking for at least ≥ 1 year) Never smokers (conventional combustible tobacco cigarette) The authors concluded that peri-implant health was more compromised among cigarette smokers than vaping individuals and non-smokers. Increased levels of proinflammatory cytokines in cigarette smokers and vaping individuals may suggest greater peri-implant inflammatory response.
Huilgol *et al.* [259] 2019	Harm	The authors reported on the relationship between **e-cigarette use,** defined as daily or intermittent use within 30 days prior to survey administration, and **poor oral health** (the number of permanent teeth removed due to non-traumatic causes). *Comparative groups* E-cigarettes users themselves (daily, some days, intermittent use in last 30 days) Conventional combustible tobacco cigarette users (current daily, some days, intermittent use) Non-users (conventional combustible tobacco cigarettes in last 30 days) Non-users (e-cigarettes in last 30 days) In multivariable analysis, daily e-cigarette use was independently associated with 78% higher odds of poor oral health (AOR: 1.78; 95% CI: 1.39–2.30; p<0.001). The authors concluded that daily, but not intermittent, use of e-cigarettes was independently associated with poor oral health.
Jeong *et al.* [257] 2020	Harm	The authors reported on the association of conventional combustible tobacco cigarette smoking and **e-cigarette vaping with periodontal disease.** *Comparative groups* E-cigarettes users themselves E-cigarettes users themselves (former) Conventional tobacco cigarette users Non-users (e-cigarette) Non-users (any products) The authors concluded that e-cigarette and conventional combustible tobacco cigarette use were both significantly associated with increased periodontal disease rates. After adjusting for demographic, socioeconomic, and health-related characteristics, both vaping and smoking had a

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on oral diseases
		significant association with periodontal diseases. The authors suggested that vaping may not be a safe alternative to smoking.
Vora *et al.* [258] 2019	Harm	The authors reported on the relationship between smoking behaviours – specifically cigarette smoking and using other types of **tobacco products – and self-reported gingival disease.** *Comparative groups* E-cigarettes users themselves who never smoked (current) Conventional combustible tobacco cigarette users (ever and current) Conventional combustible tobacco cigarette users (former stopped ≤12 months) Conventional combustible tobacco cigarette users (former stopped > 12 months) Cigar users (regular) Pipe users (regular) Hookah users (regular) Other tobacco product users (smokeless tobacco products, chewing tobacco, snuff, snus, or dissolvable tobacco) (regular) Poly product users (conventional combustible tobacco cigarette, cigar, pipe and/or hookah) Experimenters (currently using cigarettes, e-cigarettes, cigar products, pipes, hookah, or smokeless tobacco products, but used fewer than 100 times) The authors concluded that numerous tobacco use patterns were associated with worse periodontal health compared with tobacco never users.
		Markers of infection
Cichonska *et al.* [262] 2019	Harm	The authors reported on the relationship between **e-cigarettes** and **selected antibacterial properties of saliva** (IgA, lysozyme, and lactoferrin levels). *Comparative groups* E-cigarettes users themselves (daily for ≥ 6 months) Conventional combustible tobacco cigarette users (≥ 10 per day for≥ 6 months) Non-smokers (conventional combustible tobacco cigarette) The authors concluded that the saliva of e-cigarette users showed changes in antibacterial properties in comparison with the control group and with conventional combustible tobacco cigarette smokers. More specifically, among e-cigarette users, statistically significant differences were observed in levels of lysozyme and lactoferrin; however, no statistically significant differences for the IgA levels were found.
Mokeem *et al.* [263] 2019	Harm	The authors reported on the relationship between **oral *Candida albicans* carriage**, number of missing teeth, and unstimulated whole salivary flow rate with smoking-related behaviours, specifically among cigarette and water pipe smokers, **e-cigarette users**, and never-smokers. *Comparative groups* E-cigarettes users themselves Conventional combustible tobacco cigarette users (daily) Never smokers (conventional combustible tobacco cigarette) Water pipe smokers ≥ 1 time per day for ≥12-months The authors concluded that oral *Candida albicans* carriage was significantly higher among cigarette and water pipe smokers and e-cigarette users than among never-smokers. No significant differences were identified among groups in the oral carriage of other Candida species.
Stewart *et al.* [264] 2018	Neither harm nor benefit	The author reported the effects of tobacco smoke and **e-cigarette vapour** exposure on the **oral and gut microbiota** in humans. *Comparative groups* E-cigarettes users themselves (daily) Conventional combustible tobacco cigarette users (daily) Matched controls (matching variables not reported) The author concluded that people who regularly use e-cigarettes do not have measurably different oral or gut bacterial communities compared to non-smokers.

4.3.1.2.6 Developmental and reproductive effects: cross-sectional surveys

There were no cross-sectional surveys on the relationship between e-cigarettes and developmental and reproductive effects.

4.3.1.2.7 Injuries and poisonings: cross-sectional surveys

There were no cross-sectional surveys on the relationship between e-cigarettes and injuries or poisonings.

4.3.1.2.8 Exposure to e-cigarette toxins: cross-sectional surveys

There were nine cross-sectional survey papers grouped under exposure to e-cigarette toxins (Table 37). They measured toxins in e-cigarettes alone, toxins and carcinogens in e-cigarettes compared to conventional tobacco cigarettes, organophosphates entering the body from e-cigarettes, and polycyclic aromatic hydrocarbons (which are environmental pollutants). Some of the categories of toxins measured were: urinary nicotine metabolites, minor tobacco alkaloids, arsenic and arsenic compounds, tobacco-specific nitrosamines, metals, polycyclic aromatic hydrocarbons, and volatile organic compounds.

One study concluded that tobacco smoke was a source of toxic elements such as copper, zinc, antimony, strontium, and vanadium.[266] E-cigarette aerosol seemed to be a new source for intake of other toxic elements, such as silver, tin, and rare earth elements such as cerium, erbium, and gadolinium.[266] The outcomes assessed in this study were limited to participants blood toxin levels.

Four studies examined the toxicity of conventional tobacco cigarettes compared with e-cigarettes. The first study concluded that compared with cigarette smokers, people using e-cigarettes have lower levels of the urinary toxicant and carcinogen metabolites measured in their study.[267] The second study concluded that using conventional tobacco cigarettes alone or in combination with e-cigarettes is associated with higher concentrations of potentially harmful tobacco constituents in comparison with using e-cigarettes alone.[268] However, the lowest levels of harmful tobacco constituents were in non-users. The third study concluded that smokers who completely switched to e-cigarettes and quit smoking tobacco cigarettes may significantly reduce their exposure to cadmium, and probably to lead.[269] By contrast, the fourth study concluded that the observed levels of blood cadmium, lead, and mercury among USA participants aged 12 years or over did not differ among cigarette smokers only, e-cigarette users only, and dual users of both cigarettes and e-cigarettes.[270]

One study reported that although e-cigarette vapour may be less hazardous than tobacco smoke, findings challenged the idea that e-cigarette vapour is safe, because many of the volatile organic compounds identified within the vapour are carcinogenic.[271]

The authors of one study found nickel in urine and saliva, and chromium in saliva.[272] Both were positively associated with concentrations of the corresponding metals in aerosol samples collected from the vapour of the participants' personal vaping devices, providing strong evidence that metals present in the aerosol were inhaled by the users.

One study reported that four organophosphate flame retardants were detected in a much higher proportion of smokeless tobacco users (including e-cigarette users) than in cigarette smokers and non-users.[273]

Polycyclic aromatic hydrocarbons are associated with environmental pollution and their biomarkers were examined in one study.[274] Cigarette users had the highest geometric mean levels of polycyclic aromatic hydrocarbons compared with other tobacco product users, and, not surprisingly, non-users had the lowest mean levels. Smokeless tobacco product users and e-cigarette users had levels of polycyclic aromatic hydrocarbon biomarkers that fell somewhere between the levels found in tobacco users and in non-users.

Table 37 Cross-sectional survey papers on exposure to e-cigarette toxins, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on exposure to e-cigarette toxins
Hecht *et al.* [267] 2015	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **relationship between e-cigarette** smokers who had not smoked tobacco cigarettes for at least 2 months and the presence of **a suite of toxicant and carcinogen metabolites**, including: 1-hydroxypyrene (1-HOP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), 3-hydroxypropylmercapturic acid (3-HPMA), 2-hydroxypropylmercapturic acid (2-HPMA), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), S-phenylmercapturic acid (SPMA), nicotine, and cotinine. *Comparative groups* E-cigarettes users themselves (exclusive for 2 months) (former) Conventional combustible tobacco cigarette users (exclusive)) Levels of 1-HOP, total NNAL, 3-HPMA, 2-HPMA, HMPMA, and SPMA were significantly lower in the urine of e-cigarette users compared with that of cigarette smokers. Levels of nicotine and cotinine were significantly lower in e-cigarette users compared with cigarette smokers. The authors concluded, with respect to the compounds analysed in this study, that e-cigarettes have a more favourable toxicity profile than tobacco cigarettes.
Aherrera *et al.* [272] 2017	Harm	The authors reported on the relationship between **e-cigarettes** and **the metals nickel and chromium, which are components of the devices' heating coil.** *Comparative groups* E-cigarettes users themselves (exclusive daily for ≥ 6 weeks in never smokers or quitters ≥ 3 months) Dual users (used combustible cigarettes at least weekly and e-cigarette users daily for ≥ 6 weeks) The authors concluded that the study of daily e-cigarette users indicates that metals in e-cigarette aerosol are inhaled and absorbed into the bodies of users, representing a relevant contributor to metal internal dose. As the first study to make direct comparisons between source and metal biomarkers from e-cigarette use, the authors found that nickel in urine and saliva and chromium in saliva were positively associated with concentrations of the corresponding metals in aerosol samples collected from users' personal vaping devices, providing strong evidence that metals present in the aerosol are inhaled by the user. E-cigarette use patterns – such as more e-liquid consumed per week, a shorter time between waking and first vape, and a higher voltage used – were also associated with higher nickel biomarker levels.
Badea *et al.* [266] 2018	Harm	The authors reported on the relationship between non-smokers, cigarette smokers, and **e-cigarette users** with the presence of a **range of inorganic elements**. Serum concentration levels of 43 elements, including trace elements and other rare earth elements and minor elements considered pollutants were measured. *Comparative groups* E-cigarettes users themselves (former smokers) Conventional combustible tobacco cigarette users (daily) Non-users (conventional combustible tobacco cigarette) The authors concluded that tobacco smoke is a source of toxic elements such as copper, zinc, antimony, strontium, and vanadium, and that e-cigarettes seem to be a new source for intake of silver, tin, and rare earth elements such as cerium, erbium, and gadolinium.
Goniewicz *et al.* [268] 2018	Less harmful than conventional combustible	The authors reported on estimates of biomarker concentrations in combustible cigarette users, **e-cigarette users**, dual users, and never tobacco users of **tobacco-related toxicant concentrations**. *Comparative groups* E-cigarettes users themselves (exclusive, daily or someday) Conventional combustible tobacco cigarette users (exclusive, daily or someday)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on exposure to e-cigarette toxins
	tobacco cigarettes	Dual users (e-cigarettes and conventional combustible tobacco cigarette users, exclusive, daily or someday) Never users (conventional combustible tobacco) The authors concluded that the findings provide evidence that using combustible tobacco cigarettes alone or in combination with e-cigarettes is associated with higher concentrations of potentially harmful tobacco constituents in comparison with compared to e-cigarettes alone.
Prokopowicz *et al.* [269] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **e-cigarettes and levels of cadmium and lead**. *Comparative groups* E-cigarettes users themselves (≥ 6 months, and former smokers for ≥ 6 months,) Conventional combustible tobacco cigarette users (daily for ≥ 2 years) Dual users (e-cigarettes for ≥ 6 months and smoked conventional tobacco cigarettes for ≥ 2 years) Non-smokers The authors concluded that smokers who completely switched to e-cigarettes and quit smoking conventional combustible tobacco cigarettes may significantly reduce their exposure to cadmium, and probably to lead.
Rubinstein *et al.* [271] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on a **range of chemical toxicants** (metabolites of benzene, ethylene oxide, acrylonitrile, acrolein, propylene oxide, acrylamide, and crotonaldehyde) in two groups, **e-cigarette**-only users and never-using controls. *Comparative groups* E-cigarettes users themselves (current, ≥ 1 time past 30 days and ≥ 10 times in lifetime) Conventional combustible tobacco cigarette users (current) Dual users (e-cigarettes and smoked conventional tobacco cigarettes) Never-using controls The authors concluded that although e-cigarette vapour may be less hazardous than tobacco smoke, their findings challenged the idea that e-cigarette vapour is safe, because many of the volatile organic compounds identified are carcinogenic.
Wei *et al.* [273] 2018	Harm	The authors reported on the relationship between **e-cigarette** users and **metabolite levels of flame retardants** (and their urinary metabolites. Four metabolites had detection rates >60%, the authors observed higher adjusted geometric mean for (bis(2-chloroethyl) phosphate (BCEP)), a metabolite of tris(1-chloro-2-propyl) phosphate (bis(1-chloro-2-propyl) phosphate), tris(2-chloroethyl) phosphate (TCEP), in the users of e-cigarettes than in both non-users and cigarette users, suggesting that using e-cigarettes could lead to elevated exposure to TCEP. In a similar fashion, cigar users may have a higher exposure to triphenyl phosphate (TPhP) while smokeless tobacco (including e-cigarette) users showed higher exposure to tributyl phosphate (TBUP), but lower exposure to triphenyl phosphate. *Comparative groups* E-cigarettes users themselves (exclusive, ≥ 1 in last 5 days) Conventional combustible tobacco cigarette users (exclusive, ≥ 1 in last 5 days) Non-user (any tobacco products) Cigar users (exclusive, frequency of use in last 5 days) Smokeless tobacco products users (exclusive, frequency of use in last 5 days) The authors concluded that while the results are preliminary, they indicate a need for a better examination of the types and levels of organophosphate flame retardants and their potential contamination sources in non-cigarette tobacco products, including e-cigarettes.
Jain [270] 2019	Harm	The author reported on **concentrations of cadmium, lead, and mercury in blood** among cigarette, cigar, **e-cigarette**, and dual cigarette and e-cigarette users in the USA. *Comparative groups* E-cigarettes users themselves (frequency of use in last 5 days)

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on exposure to e-cigarette toxins
		Conventional combustible tobacco cigarette users (frequency of use in last 5 days) Dual users (e-cigarettes and conventional tobacco cigarettes) Non-smokers (for the last five days) Cigars users only (frequency of use in last 5 days) The author concluded that the observed levels of blood cadmium, lead, and mercury among persons in the USA aged **12 years or over** were not found to differ among cigarette-only users, e-cigarette-only users, and dual users of both cigarettes and e-cigarettes.
Wang *et al.* [274] 2019b	Harm	The authors reported on the relationship between **smoking behaviours in adults and environmental pollutants of polycyclic aromatic hydrocarbons**. *Comparative groups* E-cigarettes users themselves (exclusive, current) Conventional combustible tobacco cigarette users (exclusive, current) Smokeless product users (exclusive, current) Other single tobacco product users (exclusive, current) Dual users (combustible products users and non-combustible products users) Dual and poly users (any other dual or multiple product users) Never users (of any tobacco product) Geometric mean (GM) concentrations and evaluated associations between tobacco product user categories and **polycyclic aromatic hydrocarbon** biomarker concentrations were reported. For all biomarkers examined, cigarette users had the highest geometric means compared to other tobacco product users. Interestingly, geometric means of 2-hydroxyfluorene, 3-hydroxyfluorene, and 2,3-hydroxyphenanthrene were significantly higher in exclusive smokeless product users than in e-cigarette users; 3-hydroxyfluorene and 1-hydroxypyrene were also significantly higher in e-cigarette and exclusive smokeless product users than in never users. Everyday cigarette and exclusive smokeless product users had significantly higher geometric means for most biomarkers than sometimes users; cigarette and exclusive smokeless product users who had used the product in the last hour had significantly higher geometric means of most biomarkers than other occasional cigarette or exclusive smokeless product users. By contrast, everyday e-cigarette users' geometric means of most biomarkers did not differ significantly from those in sometimes e-cigarette users.

4.3.1.2.9 Other outcomes: cross-sectional surveys

The 11 cross-sectional survey papers where the reported outcomes did not align with the adapted Academies of Sciences' umbrella terms included papers on the endocrine system, sensory organs, metal contaminates, and adverse events (Table 38). The endocrine system papers examined e-cigarette use and measures of self-reported diagnosis of prediabetes and clinically assessed glycated haemoglobin levels. One paper reported that there was an indirect association between e-cigarette smoking and glycated haemoglobin levels (HbA1c) levels in e-cigarette users and dual users, compared with levels among non-smokers.[275] Physically inactive and overweight males who vaped had higher HbA1c levels. Another paper reported that current e-cigarette users had increased odds of reporting a diagnosis of prediabetes compared to never e-cigarette users.[276]
The sensory organ system paper included an ophthalmic assessment of tear function.[277] This study concluded that e-cigarette vapers were more likely to show moderate to severe symptomatic dry eye and poorer tear film quality compared with non-smokers.

The papers on metal contaminates included secondary or subsequent exposure to e-cigarette contaminates among non-e-cigarette users. One paper concluded that non-users living in homes with e-cigarette users were passively exposed to, and absorbed, nicotine.[278] Another paper concluded that almost four out of five neonatal intensive care unit medical staff had measurable finger nicotine, leading to third-hand nicotine contamination in infant patients.[279]

One paper examined any spending on e-cigarettes among e-cigarette users, and reported that, after controlling for confounding factors, the odds of negative health outcomes were similar and occurred whether the participant had purchased the e-cigarettes or not.[280]

One paper concluded that dual users were significantly more likely to report adverse events of vaping than e-cigarette-only users.[281] Experiencing health improvements was significantly more likely among e-cigarette-only users than among dual users for all surveyed physiological functions.

Two papers reported that subjective experiences at first use differ by tobacco product, [282] and one paper reported that adolescents who had tried e-cigarettes reported fewer negative symptoms from their first e-cigarette than from their first conventional cigarette. [283]

One paper described experiences of e-cigarette-related adverse events (such as a 'dry puff') and undesirable events (such as leaking).[284]

Table 38 Cross-sectional survey papers on other outcomes, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on other outcomes
Ballbe *et al.* [278] 2014	Harm	The authors reported on the relationship between **passive exposure** to **nicotine** in conventional combustible tobacco cigarettes and **e-cigarettes** in 54 non-smoker volunteers from different homes. *Comparative groups* E-cigarettes users themselves (Passive exposure (living at home with conventional combustible tobacco cigarette users) Passive exposure (living at home without conventional combustible tobacco cigarette users) The authors concluded that non-smokers passively exposed to e-cigarettes absorb nicotine.
Chen *et al.* [283] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on how symptoms that adolescents experience during their first time using a cigarette predict their current use, but little is known about the **symptoms experienced during first e-cigarette use**. *Comparative groups* E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current) Dual users (e-cigarettes and conventional combustible tobacco cigarette) Non-users (not current) The symptoms were coded as negative (felt bad, coughing/chest pain, bad taste in mouth, upset stomach, and dizzy/lightheaded, with a range from 0 to 5) and positive (rush/buzz, and felt relaxed, with a range from 0 to 2) symptoms from their first cigarette and e-cigarette use. Of the 29 adolescents who had tried conventional combustible tobacco cigarettes, 28 had reported results, 22 (76%) reported experiencing negative symptoms only, 2 (7%) reported feeling neutral only, and 4 (14%) reported experiencing both positive and negative symptoms. No participants reported positive symptoms only. The negative symptoms that adolescents reported included feeling dizzy, sick, bad taste in their mouth, difficulty breathing, and headache. By contrast, of the 29 adolescents who had tried e-cigarettes, 9 (31%) reported experiencing negative symptoms only, 12 (41%) reported feeling neutral only, 6 (21%) reported experiencing positive symptoms only, and 2 (7%) reported experiencing both positive and negative symptoms. Twenty-five of the 29 adolescents (86%) reported that they felt 'normal', 'no change', or 'the same' after their first e-cigarette. Adolescents reported fewer negative symptoms from their first e-cigarette than from their first cigarette, and e-cigarette symptoms did not influence use as they do for cigarettes.
Mantey *et al.* [282]	Less harmful than conventional	The authors reported on the relationship between cigarette**, e-cigarette**, hookah, and cigar products and **symptoms at first use** (nausea, coughing, relaxation, rush/buzz, and dizziness).

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on other outcomes
2017	combustible tobacco cigarettes	*Comparative groups* E-cigarettes users themselves Conventional combustible tobacco cigarette users Hookah users Cigar users The authors concluded that subjective experiences at first use differ by tobacco product.
Yao *et al.* [280] 2017	Harm	The authors examined the relationship between **spending on e-cigarettes**, **30-day e-cigarette use,** and **disease symptoms** among current adult cigarette smokers. *Comparative groups* E-cigarettes users themselves (ever) E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (< 5 years ago) The authors reported that those who spent money on e-cigarettes were more likely to report chest pain (AOR: 1.25; 95% CI: 1.02–1.52), to notice blood when brushing their teeth (AOR: 1.23; 95% CI: 1.02–1.49), to have sores or ulcers in their mouth (AOR: 1.36; 95% CI: 1.08–1.72), and to have more than one cold (AOR: 1.36; 95% CI: 1.05–1.78) than those with no spending on e-cigarettes in the past 30 days in an adjusted analysis. After controlling for cigarettes smoked per day and other covariates, there were no significant relationships between 30-day e-cigarette use and symptoms.
Choi *et al.* [275] 2018	Possible harm	The authors reported on the relationship between **smoking behaviour patterns and glycated haemoglobin levels**. *Comparative groups* Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Dual users (e-cigarette and conventional combustible tobacco cigarette) Non-smoker (conventional combustible tobacco cigarette users) In the reported findings, elevated **glycated haemoglobin levels** (HbA1c) levels were observed among subjects who were dual users of e-cigarettes and conventional combustible tobacco cigarettes and who were e-cigarette-only or conventional combustible tobacco cigarette-only users, compared with those among non-smokers; however, a direct association between e-cigarette use and HbA1c levels was not reported. In the analyses stratified by sex, men who were dual users and e-cigarette only or conventional combustible tobacco cigarette-only users had higher HbA1c levels than non-smokers, whereas among women, there were no significant results. Among physically inactive subjects, dual users were more strongly associated with elevated HbA1c levels. However, it remains unclear whether e-cigarette use alone can induce an increase in HbA1c levels. According to body mass index, dual users had a strong association of elevated HbA1c levels among people who were obese and overweight compared with those who were average weight and underweight.
Kyriakos *et al.*[284] 2018	Harm	The authors reported on the characteristics and correlates of **e-cigarette product attributes and undesirable events** during use. *Comparative groups* E-cigarettes users themselves (ever) E-cigarettes users themselves (current, daily and weekly) E-cigarettes users themselves (current, less than weekly) The authors reported that current daily or weekly prevalence of e-cigarette use among a sample of adult smokers was 7.5%. The most common attributes of e-cigarettes used included those that are flavoured, contain nicotine, and are of tank style. Use of e-liquid refill nozzle caps, described as easy for a child to open, was associated with spilling during refill. Participants who occasionally or regularly adjusted the power (voltage) or temperature of their e-cigarette had greater odds

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on other outcomes
		of ever experiencing a 'dry puff'. Mixing different e-liquids was associated with leaking during use and spilling during refill. The authors concluded that ongoing evaluation of factors associated with e-cigarette attributes, and of the correlates of experiencing undesirable events during e-cigarette use to product design, is crucial to monitoring the impact of the implementing Acts of the EU Tobacco Products Directive.
Abafalvi *et al.*[281] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **e-cigarette**-only users and dual e-cigarette and conventional combustible tobacco cigarette users with a range of 16 **adverse events** and 10 **physiological functions**. *Comparative groups* E-cigarette users themselves (former smokers who had switched completely to e-cigarettes, with detail on daily past use of conventional combustible tobacco cigarette recorded; and detail on frequency and duration of e-cigarette use and nicotine content) Dual users (e-cigarettes, combustible tobacco cigarettes users) Excluded never smokers The authors concluded that the dual users were significantly more likely to report adverse events of vaping than e-cigarette-only users (26.2% versus 11.8%; $p<0.001$). Experiencing health improvements was significantly more likely among e-cigarette-only users than among dual users for all surveyed physiological functions. E-cigarette-only users reported larger effects of vaping on sensory, physical functioning, and mental health factors compared with dual users.
Atuegwu *et al.*[276] 2019a	Harm	The authors reported on the association of **e-cigarette** use with a self-reported **diagnosis of prediabetes** in never cigarette smokers. *Comparative groups* E-cigarettes users themselves (current) E-cigarettes users themselves (former) Smokeless tobacco products users (current) Never vapers (e-cigarettes) The authors concluded that e-cigarette use may be associated with self-reported prediabetes.
Chang *et al.*[285] 2019	Harm	The authors reported on the relationship between **e-cigarette use** and **self-reported health outcomes.** *Comparative groups* E-cigarettes users themselves (exclusive, current) E-cigarettes users themselves (with smokers, current) Conventional combustible tobacco cigarette users (exclusive, current) Conventional combustible tobacco cigarette users (with e-cigarette, current) *The sample was stratified into the smoking and non-smoking populations based on the status of current cigarette use. The authors concluded that some e-cigarette usage patterns were associated with poorer health conditions in smoking and non-smoking populations, but that they were cautious about making conclusive claims regarding e-cigarette usage patterns.
Md Isa *et al.*[277] 2019	Harm	The authors reported on the **tear function** in **e-cigarette** vapers. *Comparative groups* E-cigarettes users themselves (used ≥ 1-year, former combustible tobacco smokers ≥ 6 months, or e-cigarette daily users who occasionally use conventional combustible tobacco cigarette) Never smokers (with no history of smoking and smokers in their close family) The authors concluded that vapers showed moderate to severe symptomatic dry eye and poorer tear film quality compared with non-smokers. High vaping voltage may have aggravated the dry eye syndrome because of hazardous by-products from pyrolysis of the e-liquid constituents.
Northrup *et al.*[279]	Harm	The authors reported on the contribution of medical staff to **third-hand smoke contamination in a neonatal intensive care unit.** *Comparative groups*

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on other outcomes
2019		E-cigarettes users themselves (current) E-cigarettes users themselves (former) Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Never vapers (e-cigarette) Never smokers (conventional combustible tobacco cigarette) Passive exposure (living with a conventional combustible tobacco cigarette users or e-cigarette users) Passive exposure (living without a conventional combustible tobacco cigarette or e-cigarette users) The authors concluded that almost four in five neonatal intensive care unit medical staff had measurable finger nicotine, with finger surface area and frequency of reported exposure to tobacco smoke in friends' or family members' homes emerging as important correlates, leading to third-hand nicotine contamination in a neonatal intensive care unit.

4.3.2 Case-control studies: e-cigarettes

4.3.2.1 Study characterisation: e-cigarettes

There were two case-control studies that selected their cases based on the disease of interest and examined their history to identify exposures of interest.[27] The controls did not have the disease of interest but were comparable with respect to other factors of interest. The limitations of case-control studies are that they suffer from recall bias, cannot establish a temporal sequence, and have difficulty controlling for all confounding factors.

Both case-control studies were conducted in the USA and published between 2018 and 2019. Both reported harms of e-cigarette use.

The number of case-control study papers on e-cigarette harms categorised under the adapted Academies of Sciences' framework were: one under cancers (two markers for bladder cancer identified in e-cigarette users, n=23) and one under respiratory diseases (lung injury associated with tetrahydrocannabinol in e-liquid, n=585). There were no case-control study papers under the other reporting areas: 'dependence and abuse liability', 'cardiovascular diseases', 'oral diseases', 'developmental and reproductive effects', 'injuries and poisonings', 'exposure to e-cigarette toxins', and 'other outcomes'.

4.3.2.2 Harms: e-cigarettes

4.3.2.2.1 Dependence and abuse liability: case-control studies

There were no case-control studies on the relationship between e-cigarettes and dependence and abuse liability outcomes.

4.3.2.2.2 Cardiovascular diseases: case-control studies

There were no case-control studies on the relationship between e-cigarettes and cardiovascular disease outcomes.

4.3.2.2.3 Cancers: case-control studies

There was one case-control study on the relationship between e-cigarettes and bladder cancer outcomes (Table 39). Bladder carcinogenic risk was assessed through a variety of measures, including aromatic amines and polyaromatic hydrocarbon metabolites, biomarkers of nicotine, tobacco-specific N-nitrosamines (TSNAs), and a range of volatile organic compounds.[286] The specific volatile organic compounds measured were the compounds acrolein, acrylamide, acrylonitrile, 1,3-butadiene, and ethylene oxide. The authors of the study determined that e-cigarette users' urine tested positive for the presence of two carcinogenic compounds, o-toluidine and 2-naphthylamine, at a mean 2.3-fold and 1.3-fold higher concentration, respectively, than that observed in the bladder cancer controls. According to the authors, this highlights the need to better understand the safety profile of e-cigarettes with respect to bladder cancer.

Table 39 Case-control study papers on cancers, benefits or harms

Author(s), year	Possible benefit or harm	Case-control study papers on cancers
Fuller *et al*. [286] 2018	Harm	The authors reported on the relationship between non-cigarette smoking e-cigarette-only users and non-smoking, non-e-cigarette-using controls with known bladder carcinogenic aromatic amines and polyaromatic hydrocarbon metabolites in order to understand the risk profile of e-cigarette use and bladder cancer. Age: mean age of 39.4 years. Sex: male (69.2%). Country: USA. Data source: Not reported. Population size: 23. *Comparative groups* E-cigarettes users themselves (some former smokers >12 months) Non- conventional combustible tobacco cigarette users Outcomes: Participants were tested for urinary aromatic amines and polyaromatic hydrocarbon metabolites. Specifically, samples were analysed for the noncarcinogenic marker of polyaromatic hydrocarbon exposure 1-hydroxypyrene; for carcinogenic polyaromatic hydrocarbons, including benz(a)anthracene and benzo(a)pyrene; and for the carcinogenic aromatic amines o-toluidine and 2-naphthylamine. Analysis of e-cigarette users' urine revealed the presence of two carcinogenic compounds, o-toluidine and 2-naphthylamine, at a mean 2.3-fold and 1.3-fold higher concentration (p=0.0013 and p=0.014, respectively) than that observed in the controls. The authors identified the need to better understand the safety profile of e-cigarettes and their contribution to the development of bladder cancer given the observed greater concentration of carcinogenic aromatic amines in the urine of e-cigarette users. Device and products: Not reported

4.3.2.2.4 Respiratory diseases: case-control studies

There was one case-control study on the relationship between e-cigarettes and respiratory disease outcomes, specifically lung injury (Table 40). The paper identified risk factors of e-cigarette products used by patients in Illinois and examined whether e-cigarette use behaviours differed between adult e-cigarette-associated lung injury patients (cases) and adults who used these products but did not develop lung injury (controls).[287] The e-cigarette use behaviours of 66 e-cigarette-associated lung injury patients aged 18–44 years who were interviewed as part of the ongoing outbreak investigation were compared with a subset of 519 survey respondents aged 18–44 years who reported use of tetrahydrocannabinol-containing e-cigarettes. Compared with these survey respondents, e-cigarette-associated lung injury patients had higher odds of reporting exclusive use of tetrahydrocannabinol-containing products, using e-cigarettes frequently, and obtaining e-cigarettes from informal sources. The odds of using Dank Vapes, a class of largely counterfeit tetrahydrocannabinol-containing products, was much higher among lung injury patients than among controls.

Table 40 Case-control study papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case-control study papers on respiratory diseases
Navon *et al.* [287] 2019	Harm	In the *Morbidity and Mortality Weekly Report* of the US Department of Health and Human Services and Centers for Disease Control and Prevention, first posted in November 2019, the authors reported on risk factors of e-cigarette, or vaping, products used by patients in Illinois. *Comparative groups* E-cigarettes users themselves (nicotine) E-cigarettes users themselves (tetrahydrocannabinol and nicotine). The Illinois Department of Public Health conducted an online public survey between September and October 2019 targeting e-cigarette, or vaping, product users in Illinois, examining whether e-cigarette, or vaping, product use behaviours differed between adult e-cigarette, or vaping, product use-associated lung injury patients and adults who used these products but did not develop lung injury. Among 4,631 survey respondents, 94% reported using any nicotine-containing e-cigarette, or vaping, products in the past 3 months; 21% had used any tetrahydrocannabinol-containing products; and 11% had used both tetrahydrocannabinol-containing products and nicotine-containing products. The prevalence of tetrahydrocannabinol-containing product use was highest among survey respondents aged 18–24 years (36%) and decreased with increasing age. E-cigarette, or vaping, product use behaviours of 66 e-cigarette, or vaping, product use-associated lung injury patients aged 18–44 years who were interviewed as part of the ongoing outbreak investigation were compared with a subset of 519 survey respondents aged 18–44 years who reported use of tetrahydrocannabinol-containing e-cigarette, or vaping, products. Compared with these survey respondents, product use-associated lung injury patients had higher odds of reporting exclusive use of tetrahydrocannabinol-containing products (AOR: 2.0; 95% CI: 1.1–3.6); frequent use (more than five times per day) of these products (AOR: 3.1; 95% CI: 1.6–6.0); and obtaining these products from informal sources, such as a dealer, off the street, or from a friend (AOR: 9.2; 95% CI: 2.2–39.4). The odds of using Dank Vapes, a class of largely counterfeit tetrahydrocannabinol-containing products, was also higher among e-cigarette, or vaping, product use-associated lung injury patients (AOR: 8.5; 95% CI: 3.8–19.0). Device and products: Any nicotine-containing products. Only nicotine-containing products. Any nicotine-containing product <1x/day§. Any nicotine-containing product >5x/day. Any tetrahydrocannabinol-containing products. Only tetrahydrocannabinol-containing products. Any tetrahydrocannabinol-containing product <1x/day§. Any tetrahydrocannabinol-containing product >5x/day§. Dank Vapes*. Obtained any tetrahydrocannabinol-containing product informally**. Both tetrahydrocannabinol- and nicotine-containing products. * Dank Vapes are a class of largely counterfeit THC-containing products of unknown provenance that are marketed under a common name and distributed through informal sources. ** Obtaining any tetrahydrocannabinol-containing e-cigarette, or vaping, products from informal sources (a dealer, off the street, or from a friend) was compared with obtaining any tetrahydrocannabinol-containing products from a formal source (store or licensed dispensary). Because online sources might be formal (e.g. a licensed dispensary) or informal, persons who reported online purchases were excluded from this analysis. Fewer than 1% of public survey respondents reported online purchases.

4.3.2.2.5 Oral diseases: case-control studies

There were no case-control studies on the relationship between e-cigarettes and oral disease outcomes.

4.3.2.2.6 Developmental and reproductive effects: case-control studies

There were no case-control studies on the relationship between e-cigarettes and developmental and reproductive effect outcomes.

4.3.2.2.7 Injuries and poisonings: case-control studies

There were no case-control studies on the relationship between e-cigarettes and injury and poisoning outcomes.

4.3.2.2.8 Exposure to e-cigarette toxins: case-control studies

There were no case-control studies on the relationship between e-cigarettes and exposure to e-cigarette toxins outcomes.

4.3.2.2.9 Other outcomes: case-control studies

There were no case-control studies on the relationship between e-cigarettes and other outcomes

4.3.3 Longitudinal cohort studies: e-cigarettes

4.3.3.1 Study characterisation: e-cigarettes

There were 22 papers categorised as longitudinal cohort studies. In these longitudinal studies, the investigators measured e-cigarette exposure(s) in the study participants at baseline and the outcome(s) (benefit or harm) at each follow-up.[27] People with the outcome(s) of interest at baseline are excluded from the cohort. Cohort studies are useful for measuring incidence of outcomes in a population and comparing the incidence of outcomes by exposure status. However, incidence calculations require an adequate sample size in order to create a meaningful estimate. Cohort studies can establish a dose response and temporal sequence. However, they have difficulty controlling for the influence of confounding factors on the outcome of interest.

The studies were completed on populations living in France (n=1), Italy (n=10), Saudi Arabia (n=1), the UK (n=1), and the USA (n=9). The longitudinal cohort study sample sizes for analysis ranged from 16 to 30,818. The follow-up periods were between 4 and 48 months. The studies were published between 2013 and 2019.

Half of the longitudinal cohort studies (10 out of 22) were categorised under the Academies of Sciences' framework heading dependence and abuse liability. The number of longitudinal cohort study papers categorised under the adapted Academies of Sciences' framework were: 10 under dependence and abuse liability, 3 under cardiovascular diseases, 5 under respiratory diseases, 3 under oral diseases, and 1 under developmental and reproductive effects. There were no longitudinal cohort study papers under the reporting areas 'cancers', 'injuries and poisonings', 'exposure to e-cigarette toxins', or 'other outcomes'.

The summary tables for longitudinal cohort studies are presented under the adapted Academies of Sciences' headings in Sections 4.3.3.2.1 to 4.3.3.2.9 These summary tables present the authors, study objectives, and concluding summary findings. For longitudinal cohort studies, tables with additional details are presented in Appendix 4.

4.3.3.2 Harms, harm reduction, and benefits: e-cigarettes

The harms associated with e-cigarette use identified under the heading dependence and abuse liability, and investigated in longitudinal cohort studies, were: dependence, depression, dual use of conventional tobacco cigarettes and e-cigarettes, and weight control. There were higher rates of chronic respiratory diseases in e-cigarette users than in non-users, and rates of chronic respiratory diseases in smokers, vapers, and dual users (of e-cigarettes and conventional tobacco cigarettes) were similar. Under the oral diseases heading, e-cigarette users had poorer dental and periodontal health compared with non-users. One paper under the developmental and reproductive effects heading identified that new-born infants of e-cigarette users were small for gestational age. A second paper based on prospective longitudinal study design and published after the mapping search period did not uphold the first longitudinal study findings.[288]

A number of longitudinal cohort studies identified that e-cigarettes were less harmful than conventional tobacco cigarettes. For example, one study found that the use of e-cigarettes decreased cigarette consumption by 50% without causing significant nicotine withdrawal symptoms or increasing negative mental health symptoms in chronic schizophrenic patients who smoked and did not intend to quit. Another study reported that there was only a modest weight increase associated with switching from tobacco cigarettes to e-cigarettes. In addition, there was a reduction in asthma and chronic obstructive pulmonary disease symptoms after tobacco cigarette smokers switched to e-cigarette vaping. Under the oral diseases heading, e-cigarette users had lower levels of dental and periodontal diseases compared with tobacco cigarette smokers.

The authors of two longitudinal cohort studies proposed that e-cigarettes may be beneficial relative to conventional cigarette smoking. The first benefit was the possibility that their use may facilitate better blood pressure control than would be facilitated by continued tobacco cigarette smoking. The second benefit was described as a state of stable dependence, which other observers may classify as a harm.

4.3.3.2.1 Dependence and abuse liability: longitudinal cohort studies

There were 10 longitudinal cohort study papers reporting a range of measures of behaviours and personality traits among e-cigarette users associated with dependence and abuse (Table 41) These included mental health issues associated with e-cigarette use (such as depression), patterns of e-cigarette use (such as populations using e-cigarettes, smoking cessation, and relapsing behaviours), and dependence (via self-reported behaviours and measures of urinary cotinine levels). Other outcomes measured were 3-hydroxycotinine level, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) level, and changes in weight.

The studies under this heading were grouped into three themes: e-cigarette use and conventional tobacco cigarette smoking status, e-cigarettes' association with mental health, and e-cigarettes and weight gain.

Two studies reported that e-cigarettes were strongly associated with conventional tobacco cigarette use and that many e-cigarette users were dual users (i.e. they used both e-cigarettes and tobacco cigarettes).[289 290] Another two studies reported that nicotine e-cigarette use led to a state of stable dependence.[291] One study found that e-cigarette use decreased conventional tobacco cigarette consumption by 50% without causing significant nicotine withdrawal symptoms or increasing negative mental health symptoms in chronic schizophrenic patients who smoked and did not intend to quit.[292] One study reported changed puffing topography to maintain nicotine levels. [293]

In three studies, e-cigarette use was associated with depression. Three studies reported that as depressive symptoms increased, so did e-cigarette use.[294 295 296] One study reported that onset of depression was associated with onset of e-cigarette use.[295]

In one study, the authors concluded that there was no evidence of post-cessation weight increase in those who substantially reduced cigarette consumption by switching to using both conventional tobacco cigarette use and e-cigarettes (dual users), and only modest post-cessation weight increase was reported in exclusive e-cigarette users at 12-month follow-up.[297]

Table 41 Longitudinal cohort study papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on dependence and abuse liability
		Smoking status
Caponnetto *et al.* [292] 2013	Benefit	The authors reported on the relationship **of e-cigarette use with smoking reduction and smoking cessation**. *Comparative groups* E-cigarettes users themselves ('Categoria') Conventional combustible tobacco cigarette users (smoke ≥20 cigarettes per day for ≥10 years and not intending to quit) The authors concluded that e-cigarette use substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients who smoked and did not intend to quit. This was achieved without negative impacts on the symptoms of schizophrenia as assessed by the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms.
Manzoli *et al.* [289] 2017	Possible benefit	The authors reported on findings from a cohort study regarding **e-cigarette use effectiveness and safety** at 24 months. *Comparative groups* E-cigarettes users themselves (at least 50 puffs per week for at least 6 months) Conventional combustible tobacco cigarette users (1 tobacco cigarette per day for ≥6 months) Dual users (smoked conventional tobacco cigarettes and used e-cigarettes for ≥6 months) The authors concluded that e-cigarette use alone might support tobacco quitters in remaining abstinent from smoking. However, dual use did not improve the likelihood of quitting tobacco or e-cigarette use, but may be helpful in reducing tobacco consumption. Adverse event data were scarce and must be considered preliminary.

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on dependence and abuse liability
Du *et al.* [291] 2019	Benefit	The authors reported on changes in **e-cigarette use behaviours and dependence** in long-term e-cigarette users. *Comparative groups* E-cigarettes users themselves (exclusive for past 7 days) Poly users (e-cigarettes, other nicotine products for past 7 days) The authors concluded that findings suggest that the risk of relapse to cigarette smoking is low, and that e-cigarette-related dependence remains stable in long-term e-cigarette users.
McMillen *et al.* [290] 2019	Harm	The authors reported on the relationship between **e-cigarette use and future cigarette initiation** among never-smokers, and relapse among former smokers. *Comparative groups* E-cigarettes users themselves (ever user but not current) E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (former, quit ≥ 5 years) Never vapers (e-cigarettes) Never smokers (conventional combustible tobacco cigarette) Former combustible cigarette smokers who reported e-cigarette past-30-day users (9.3%) and e-cigarette ever users (6.7%) were significantly more likely than never users (1.3%) to have relapsed to current combustible cigarette smoking at follow-up (p<0.001). Baseline never-smokers who reported e-cigarette past-30-day use at follow-up (25.6%) and ever use (13.9%) were significantly more likely than those who had never used e-cigarettes (2.1%) to have initiated combustible cigarette smoking (p<0.001). Adults who reported past-30-day e-cigarette use (7.0%) and ever e-cigarette use (1.7%) were more likely than those who had never used e-cigarettes (0.3%) to have transitioned from never-smokers to current combustible cigarette smokers (p<0.001). E-cigarette use predicted combustible cigarette smoking in multivariable analyses controlling for covariates.
Soar *et al.* [293] 2019	Harm	The authors examined the relationship, in **exclusive vapers**, of levels of **nicotine intake** over time as nicotine e-liquid concentrations are reduced, i.e. **nicotine absorption** from e-cigarettes over a 12-month period. *Comparative groups* E-cigarettes users themselves (exclusive) The authors concluded that although the sample of experienced vapers reduced the concentration of nicotine in their e-liquid over time, they maintained their nicotine intake, possibly through self-titration via more intensive puffing. Findings suggest that there may be little benefit in reducing nicotine e-liquid concentration, since this appears to result in higher e-liquid consumption, which may incur both a financial and health cost.
		Mental health issues
Bandiera *et al.* [294] 2017	Potential harm	The authors reported on the relationship between **depressive symptoms and current e-cigarette use**. *Comparative groups* E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current) Other products users (smokeless snus, smokeless tobacco, large cigars, cigarillos/little cigars, or hookah) The authors concluded that elevated depressive symptoms predicted e-cigarette use 6 months later among a young adult college population, even after controlling for a variety of sociodemographic characteristics and the number of tobacco products used. However, they found no evidence that e-cigarette use predicted elevated depressive symptoms.
Lechner *et al.* [295] 2017	Harm	The authors reported on the relationship between **baseline depressive symptoms and onset of e-cigarette use, tobacco cigarette use, and dual use** at follow-ups. *Comparative groups* Non-vapers (e-cigarettes) at baseline Non-smokers (conventional combustible tobacco cigarette) at baseline E-cigarettes users themselves (at 6-month follow-up) Conventional combustible tobacco cigarette users (at 6-month follow-up) Dual use (e-cigarette and conventional combustible tobacco cigarette users at follow up)

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on dependence and abuse liability
		Higher baseline depressive symptoms predicted subsequent onset of tobacco cigarette use (OR: 1.024; 95% CI: 1.009−1.055), e-cigarette use (OR: 1.015; 95%CI: 1.003−1.023), and dual use of both products (OR: 1.021; 95%CI: 1.003−1.043). Sustained use of e-cigarettes over the 12-month observation period (versus non-use) was associated with a greater rate of increase in depressive symptoms over time (B=1.272; standard error [SE]=0.513; *P*=0.01). Among those who sustained use of e-cigarettes, higher frequency of use was associated with higher depressive symptoms at the final follow-up (B=1.611; *p*=0.04). The authors concluded that a bi-directional association of depressive symptoms with e-cigarette use onset across mid-adolescence was observed.
Marsden *et al.* [298] 2019	Harm	The authors reported on the association between frequency of **cigarette and alternative tobacco product use and depressive symptoms**. *Comparative groups* E-cigarettes users themselves (current, refillable devices) E-cigarettes users themselves (current, disposable devices) Conventional combustible tobacco cigarette users (current) Hookah product users (current) Smokeless tobacco products (current) Other product users (cigars cigarillos, little cigars) (current) The authors concluded, following separate examination of used refillable and disposable e-cigarettes, that the results did not provide evidence of a different association for each type of e-cigarette when cigarettes were not also used. Dual use of cigarettes with another product was associated with higher depressive symptoms for most product combinations. However, infrequent dual use of disposable e-cigarettes and cigarettes may not be associated with depressive symptoms.
Wiernik *et al.* [296] 2019	Harm	The authors reported on the relationship **between e-cigarette use and depressive symptoms** in smokers and former smokers. *Comparative groups* E-cigarettes users themselves (current, nicotine levels) E-cigarettes users themselves (former, nicotine levels) Conventional combustible tobacco cigarette users (current, nicotine levels) Conventional combustible tobacco cigarettes users (former, nicotine levels) Never-smokers nicotine levels (conventional combustible tobacco cigarettes) Never-vapers nicotine levels (e-cigarette) The authors concluded that depressive symptoms were positively associated with e-cigarette use in both cross-sectional and longitudinal analyses with a dose-dependent relationship. In addition, nicotine concentration and depressive symptoms were positively associated.
		Weight control
Russo *et al.* [297] 2018	Benefit	The authors reported on the relationship between **e-cigarette use and post-cessation weight increase**. *Comparative groups* All conventional combustible tobacco cigarette users (smoked > 20 per day at baseline) who quit or reduced smoking related behaviours): Regular e-cigarettes users at follow-up (exclusive or dual) Regular conventional combustible tobacco cigarette users at follow up (exclusive); Sustained smoking or vaping abstinence at follow-up (quitters). The authors concluded that there was no evidence of post-cessation weight increase in those who substantially reduced tobacco cigarette consumption by switching to e-cigarettes (i.e. dual users), and only modest post-cessation weight increase was reported in exclusive e-cigarette users at 12-month follow-up. By reducing weight gain and tobacco consumption, e-cigarette-based interventions may promote an overall improvement in quality of life.[297]

4.3.3.2.2 Cardiovascular diseases: longitudinal cohort studies

Three longitudinal cohort study papers examined the relationship between e-cigarettes and cardiovascular disease outcomes such as hypertension (Table 42). Measures of resting blood

pressure, levels of blood pressure control, oxygen perfusion of body tissues following surgery, heart rate, and body weight were analysed to determine cardiovascular health and its association with e-cigarette use. In addition to cardiovascular measures, respiratory measures of lung function, respiratory symptoms, fractional exhaled breath nitric oxide (FeNO), exhaled carbon monoxide (eCO), and high-resolution computed tomography of the lungs were measured.

In the first study, the authors stated that reducing cigarette smoking and taking up e-cigarettes resulted in improvements in systolic and diastolic blood pressure, as well as better blood pressure control at 6-month and 12-month follow-up.[299] Of note, the patients in both groups (43 e-cigarette smokers and 46 non-users) were also receiving antihypertensive treatment, which may explain some of the blood pressure controls observed. The second study involved 16 young people who had never smoked tobacco but had initiated e-cigarette use. The authors reported that , they did not demonstrate any additional respiratory function, lung injury, blood pressure, or heart rate concerns associated with 3.5 years of e-cigarette use when compared with matched non-users.[300] In the third study, the authors reported that the number of e-cigarette smokers were not adequate to enable measurement of the influence of e-cigarettes on cardiovascular complications following surgery, but they concluded that nicotine replacement using e-cigarettes carries similar risks as continued smoking and is not as safe as abstinence in the perioperative period in plastic surgery patients.[301]

Table 42 Longitudinal cohort study papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on cardiovascular diseases
Polosa *et al.* [299] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **relationship between smokers** with a diagnosis of **hypertension** and those who quit or reduced tobacco consumption by **switching to e-cigarettes**, and long-term improvement in resting blood pressure and in level of blood pressure control. *Comparative groups* E-cigarettes users themselves (daily for ≥10 months) Conventional combustible tobacco cigarette users (regular users) Dual users (e-cigarette and conventional combustible tobacco cigarette) The authors concluded that regular e-cigarette use may aid smokers with arterial hypertension in reducing or abstaining from cigarette smoking, with only trivial post-cessation weight gain (a finding reported on in the paper). The reduction in cigarette smoking and weight and the taking up of e-cigarettes resulted in improvements in systolic and diastolic blood pressure as well as better blood pressure control.
Polosa *et al.* [300] 2017	No harm or benefit	Authors reported-on **cardiovascular and respiratory health outcomes** blood pressure, heart rate, body weight, lung function, respiratory symptoms, fractional exhaled breath nitric oxide (FeNO), exhaled carbon monoxide (eCO), and high-resolution computed tomography of the lungs. *Comparative groups* E-cigarettes users themselves (exclusive, daily for ≥ 3 months) (never smoked) Never smokers (conventional combustible tobacco cigarette) The authors concluded that although it cannot be excluded that some harm may occur from e-cigarettes at later stages of the e-cigarette user's life, this study did not demonstrate any health concerns associated with long-term use of e-cigarettes in relatively young users who did not also smoke tobacco.
Michaels *et al.* [301] 2018	Harm	The authors examined nicotine replacement therapy (including **e-cigarettes) as a safe alternative to smoking** in plastic surgery patients. *Comparative groups* Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former, negative urine test) Conventional combustible tobacco cigarette users (former, positive urine test) Never smokers (conventional combustible tobacco cigarette) The authors concluded that nicotine replacement using e-cigarettes carries similar risks as continued smoking and is not as safe as abstinence in the perioperative period in plastic surgery patients. Importantly, patients who

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on cardiovascular diseases
		stopped smoking for the surgery had equivalent risk for postoperative complications as patients who had never smoked.

4.3.3.2.3 Cancers: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between e-cigarettes and cancer outcomes.

4.3.3.2.4 Respiratory diseases: longitudinal cohort studies

The five longitudinal cohort study papers reporting on the association between e-cigarette use and respiratory disease outcomes examined the relationship between e-cigarettes and chronic obstructive pulmonary disease, airway hyperresponsiveness, and asthma exacerbation (Table 43). Signs and symptoms of respiratory diseases and a range of respiratory function measures were assessed. In addition, information on other outcomes, such as myocardial infarction and/or angina, congestive heart failure, stroke, and any cancer were reported.

The studies on chronic respiratory diseases and symptoms indicate mixed findings as to whether e-cigarette use is better than tobacco use and worse than no nicotine use. For example, the authors of two small studies (16–18 participants) reported improvements in asthma at 6-month and 1-year follow-up, although it appears that the samples in the two studies may overlap.[302 303] In two studies examining chronic obstructive pulmonary disease and e-cigarettes, one study with 24 participants reported a benefit by switching from tobacco smoking to e-cigarettes at 6-month and 1-year follow-up[304] and the other study with 55 dual users reported harm at 1-year follow-up.[305] One study examining smoking-related diseases by type of cigarette use reported that smoking-related diseases were observed in 73 participants (8.0%) at 4-year follow-up, and that the rates of smoking-related diseases were similar in e-cigarette users, dual users (those who used both e-cigarettes and conventional tobacco cigarettes), and conventional tobacco cigarette smokers. [306]

Table 43 Longitudinal cohort study papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on respiratory diseases
Polosa *et al.* [302] 2014a	Less harmful than conventional combustible tobacco cigarettes	The authors undertook a retrospective review of **changes in** spirometry data, airway hyperresponsiveness, **asthma exacerbations,** and subjective asthma control in smoking asthmatics who **switched to regular e-cigarette use**. *Comparative groups* E-cigarettes users themselves (former daily smokers) Dual users (e-cigarette and conventional combustible tobacco cigarette) The authors reported improvements in asthma control, airway hyperresponsiveness, and pulmonary function in 18 asthmatic smokers who quit or dramatically reduced their tobacco consumption by switching to e-cigarettes.
Polosa *et al.* [303] 2016b	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between persisting long-term **benefits of smoking abstinence and reduction in asthmatic smokers who have switched to e-cigarettes**. *Comparative groups* E-cigarettes users themselves (exclusive) Dual users (e-cigarette and conventional combustible tobacco cigarette) The authors concluded that regular e-cigarette use ameliorates asthma outcomes, that these beneficial effects may persist in the long term, that similar benefits could also be noted in dual users, and that regular e-cigarette use was well tolerated.
Polosa *et al.* [304]	Less harmful than	The authors reported their evidence for **harm reduction in smokers with chronic obstructive pulmonary disease who switch to using e-cigarettes.**

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on respiratory diseases
2016c	conventional combustible tobacco cigarettes	*Comparative groups* E-cigarettes users themselves (exclusive, daily) Dual users (e-cigarettes and conventional combustible tobacco cigarettes daily) Conventional combustible tobacco cigarette users (exclusive, daily) The authors concluded that a marked reduction in cigarette consumption was observed in e-cigarette users. A significant reduction in chronic obstructive pulmonary disease exacerbations was reported in the chronic obstructive pulmonary disease e-cigarette user group, with their mean (±standard deviation) decreasing from 2.3 (±1) at baseline to 1.8 (±1; p=0.002) and 1.4 (±0.9; p<0.001) at follow-up visit 1 and follow-up visit 2, respectively. A significant reduction in chronic obstructive pulmonary disease exacerbations was also observed in e-cigarette users who also smoked conventional combustible tobacco cigarettes (i.e. dual users). Chronic obstructive pulmonary disease symptoms and ability to perform physical activities improved statistically in the e-cigarettes group at both visits, with no change in the control group (those who continued smoking conventional tobacco cigarettes).
Bowler *et al.* [305] 2017	Harm	The authors reported on the relationship between **e-cigarette use** in USA adults at risk for, or with, **chronic obstructive pulmonary disease**. *Comparative groups* E-cigarette users themselves (ever) E-cigarette users themselves (current) Conventional combustible tobacco cigarette users (current ≥10 pack years) and e-cigarettes (current) Conventional combustible tobacco cigarette users (former, ≥10 pack years) and e-cigarettes (current) Never users (conventional combustible tobacco cigarette or other tobacco products) The authors concluded that they could find no evidence supporting the use of e-cigarettes as a harm reduction strategy among current smokers with, or at risk for, chronic obstructive pulmonary disease.
Flacco *et al.* [306] 2019	Harm	The authors reported on the relationship between **e-cigarettes and a range of possibly smoking-related diseases** – such as chronic obstructive pulmonary disease, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischaemia or stroke, and any cancer – and changes in tobacco use. *Comparative groups* E-cigarettes users themselves (for≥ six months) Conventional combustible tobacco cigarette users (≥1 daily for ≥6 months) Dual users (e-cigarettes and conventional combustible tobacco cigarette for ≥ 6 months) The authors concluded that after 4 years a non-significant harm reduction was observed among e-cigarette users and dual users of e-cigarettes and conventional tobacco cigarettes. The complete switch to e-cigarettes may help tobacco quitters remain abstinent, but e-cigarette use in addition to tobacco did not increase the likelihood of smoking cessation or reduction. The rates of smoking-related diseases were similar in e-cigarette users, dual users (those who used both e-cigarettes and conventional tobacco cigarettes), and conventional tobacco cigarette smokers

4.3.3.2.5 Oral diseases: longitudinal cohort studies

Three longitudinal cohort study papers reported on the association between e-cigarette use and oral health outcomes (Table 44). The papers examined the relationship between e-cigarettes and oral disease using the following measures: full-mouth plaque index, bleeding on probing, clinical attachment loss, probing depth, gum disease, and bone loss around teeth.

The findings on dental health depended on the comparator, with two studies reporting improved dental health (reduced periodontal disease) following tobacco smoking cessation and moving to e-cigarettes, one reported follow-up at 4 months and the other at 1 year.[307 308] The third study reported

poorer dental health (increased periodontal disease and bone loss) at 2-year follow-up in e-cigarette users compared with non-users.

Table 44 Longitudinal cohort study papers on oral diseases, benefits or harms

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on oral diseases
Tatullo *et al.* [307] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **changes in periodontal health in individuals** who had ceased **tobacco cigarette** consumption and had started to use **e-cigarettes**, and a self-assessed need to smoke combustible cigarettes. *Comparative groups* E-cigarettes users themselves (for approximately 4 months, former daily smokers for < 10 years) E-cigarettes users themselves (for approximately 4 months, former daily smokers for ≥ 10 years) The authors stated that their observations revealed an interesting, growing trend, relating to plaque index, periodontal bleeding index, and papillary bleeding index, in the 110 subjects considered in this study. They reported a constant reduction of bacterial plaque on teeth surfaces from baseline at T0 to the end of the observational period at T2. More precisely, group 1 (less than 10 years smoking) subjects showed a homogeneous presence of a thin film of plaque at T0, which visibly decreased towards T1 until it completely disappeared in all of the group 1 subjects at T2. The result was more marked in group 2 subjects (more than 10 years smoking), and was characterised by a huge presence of plaque at T0. The authors also noted that many patients had reported an interesting reduction in the need to smoke.
ALHarthi *et al.* [308] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the impact of **cigarette smoking, e-cigarette use, and non-smoking** on **dental and periodontal health**: full-mouth plaque index, bleeding on probing, clinical attachment loss, and probing depth were measured at baseline and at 3 and 6 months after full-mouth ultrasonic scaling (without root surface debridement). The numbers of missing teeth were also recorded. *Comparative groups* E-cigarettes users themselves (exclusive, used for ≥1 year with) Conventional combustible tobacco cigarette users (≥ 5 daily) Never users (any tobacco product) The authors stated that a range of periodontal inflammatory parameters were worse in cigarette smokers than in individuals who vape e-cigarettes and in never-smokers following full-mouth ultrasonic scaling.
Atuegwu *et al.* [309] 2019b	Harm	The authors reported on the relationship between **e-cigarettes and periodontal disease**, specifically gum disease and bone loss around teeth. *Comparative groups* E-cigarettes users themselves (daily or some days) E-cigarettes users themselves (ever or any) Conventional combustible tobacco cigarette users (every or some days) Dual users (e-cigarettes with marijuana) The hypothesis in this study was that the use of electronic nicotine products would be associated with increased odds of gum disease and bone loss around teeth, even after controlling for use of conventional combustible tobacco cigarettes and other known risk factors. Sub-group analysis was performed to examine this association in participants who had a history of marijuana use and a history of illicit or non-prescribed drug use. The authors concluded that this was the case.

4.3.3.2.6 Developmental and reproductive effects: longitudinal cohort studies

One longitudinal cohort study paper reported on the association between e-cigarette use and developmental and reproductive effects (Table 45). The subject matter covered in the paper related to e-cigarettes and their effects on weight for gestational age at birth.[310] The authors concluded that e-cigarette use was associated with an increased risk of new-borns being small for gestational age. A

second paper based on prospective longitudinal study design and published after the mapping search period did not uphold the first longitudinal study findings.[288]

Table 45 Longitudinal cohort study papers on developmental and reproductive effects, benefits or harms

Author(s), year	Possible benefit or harm	Longitudinal cohort study papers on developmental and reproductive effects
Cardenas *et al.* [310] 2019	Harm	The authors reported on the relationship between **e-cigarette use** in pregnant women and **risk of small-for-gestational-age births.** *Comparative groups* E-cigarettes users themselves (current) Conventional combustible tobacco cigarette users (current) Conventional combustible tobacco cigarette users (former) Never vapers (e-cigarettes) Never smokers (conventional combustible tobacco cigarette) The authors concluded that e-cigarette use is associated with an increased risk of small-for-gestational-age births.

4.3.3.2.7 Injuries and poisonings: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between e-cigarettes and injuries or poisonings outcomes.

4.3.3.2.8 Exposure to e-cigarette toxins: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between e-cigarettes and exposure to e-cigarette toxins outcomes.

4.3.3.2.9 Other outcomes: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between e-cigarettes and other outcomes.

4.4 Interventional trials: e-cigarettes

4.4.1 Study characterisation: e-cigarettes

There were 86 papers grouped as interventional trials. Of these, eight (9%) were authored by the e-cigarette industry (Appendix 7). In these trials, participants were assigned the intervention (e-cigarette) by the investigator. The investigator then measured the impact of the exposure on one or more outcomes at a subsequent timepoint. Interventional trials allow quantification of the size and the direction of an intervention-outcome effect. There are several trial designs included in this mapping exercise. These are: randomised controlled trials, randomised crossover or Latin-square trials, non-randomised crossover or Latin-square trials, and non-randomised before and after studies. A proportion of the study papers which we grouped under interventional trials did not randomise participants to the intervention, or interventions to the participants. Rather, the investigator measured the factors of interest in the same individuals before and after intervention uptake similar to that of an observational study, but the difference was that the participant, once recruited, could not choose whether to be exposed or not as could be done in an observational study. These trials are better described as non-randomised before-and-after interventional trials. Another type of trial is a crossover before-and-after trials where participants are randomised to an intervention, and where comparisons are achieved through a crossover approach. Crossover trials with more than one crossover are referred to as Latin squares' crossover trials. The ideal trial is a randomised control trial with intervention(s) and their comparators are randomly allocated to two or more groups and these provide the highest level of evidence, followed by randomised crossover or Latin square trials. The lowest level of trial evidence is provided by non-randomised before-and-after trials whether they have or do not have a crossover element. The trial designs were most often conducted across a short time span, usually hours, days, or, in some cases, weeks.

Broadly speaking, trials on e-cigarettes were conducted in one of two settings: in a clinical laboratory setting or in a general community setting. Trials conducted in a laboratory setting followed a standardised protocol for determining aspects of the devices and nicotine levels to be assessed. This included issues such as the type of device (generation, battery power, voltage, coil resistance, carrier solution, and additives), the individuals' puffing frequency, and duration of exposure, along with how and when outcome measures were to be assessed. The second location was a community setting, where more often the individuals' general behaviours were observed. Here, participants were often allowed to vape in their customary manner. However, there was overlap in practices across the various trial settings with respect to the degree of fidelity or adherence to the standardised protocol – for example, with participants in a clinical laboratory setting being allowed to vape as desired, and participants in a general community setting following a specific set of e-cigarette vaping instructions.

In general, in clinical laboratory-based trials, outcomes were assessed at various timepoints, starting with baseline and then a follow-up minutes, hours, or, in a small number of cases, days after exposure to e-cigarettes. These trials measured the acute impact that e-cigarette use had on a range of outcomes within the time frame of the trial. In trials where the intervention represented the participants' e-cigarette behavioural habits, such as daily vaping as a lifestyle norm in a community setting, outcomes were assessed weeks, months, or up to 2 years after the trials commenced.

We identified some information on the e-cigarette devices used in the interventional trials in 62 of the 86 trial papers identified (Table 46). The characteristics of e-cigarette devices included: brand, model, generation, nicotine content, battery energy measure, voltage, and coil resistance. The variations in e-cigarettes tested included: disposable e-cigarettes which were not refillable, e-cigarettes which used replaceable prefilled cartridges, and tank models which were filled with liquids by the user. E-cigarettes which were disposable consisted of batteries with primary (not chargeable) cells, whereas e-cigarettes with secondary (rechargeable) cells used replaceable prefilled cartridges, or had refillable tanks. Information on charging capacity (how much charged, number of allowable times to be charged) and the battery energy (the charge a battery holds and time until recharging requirement, measured by milliampere hour [mAh]) was noted by some authors.

The 62 trials that examined health benefits and harms in people and that provided information about the e-cigarette devices used identified only 39 of a possible 611 or more e-cigarette models ever

produced,[3 4] which gives a sense of the small range of e-cigarettes tested in trials involving people that are subsequently published in peer-reviewed papers. The nicotine concentration levels were reported in several ways. Specifically, a nicotine concentration level could be reported in mg/mL, as a percentage, as an upper concentration threshold level, or as an average concentration level. Some authors reported processes where nicotine levels noted on the manufacturer's product label were independently assessed using peer-reviewed published laboratory methods, noting a difference between the concentration on the manufacturer's label and laboratory-assessed nicotine concentration levels. An alternative method of assessing nicotine was by calculating the residual e-liquid supplied to participants at specific timepoints during trial participation or at trial completion. The actual reported nicotine concentration level in supplied products varied from nicotine free (also referred to as a placebo) to a strength of 48 mg/mL. The variation in nicotine dosages is noteworthy, doubly so in trials seeking to assess issues around dependence and abuse liability, in light of reports that the higher nicotine levels, specifically reported as between 18 and 36 mg/mL in some trials, have been demonstrated to be the only doses resulting in a reliable increase in nicotine plasma concentrations. Battery energy measures varied from 90 to 5000 milliampere hour, voltage from 3.0 to 4.4 volts and coil resistance from 0.2 to 1.8-ohm. Finally, reports on the carrier solution a mixture of propylene glycol and vegetable glycerine, varied from 40.0% to 72.5% for propylene glycol and 18.8% to 40.8% for vegetable glycerine. A range of other products and their percentages in the carrier solution – such as <5% cadmium, <5% lead, <1% mercury, <5% chromium, 19.7% pyrazine, 0.13% 2,3-dimethylpyrazine, 0.10% trimentyl, and 0.15% myosmine – was also noted.

Nine (10%) of the 86 trials reported on an exposure outcome effect measured between 12 weeks and 24 months. More specifically, two (2%) trials ran for 24 months; four (5%) trials ran for 12 months; two trials had 6 months' duration, and one trial had a duration of 3 months.

The remaining 77 (90%) trials reported on outcomes gathered within 8 weeks or less. Five trials of very short duration had time period intervals between the exposure and the outcome measurement point as short as during intervention administration, or 10, 20, 30, or 50 minutes after intervention initiation.

Of the 77 short-term trials, 33 (43%) had several sessions (between two and five) with varying time periods between sessions (ranging from 24 hours to 1 week). Five trials reported a varying number of sessions (between two and four) with up to 4 weeks between the timepoints at which outcome measures were gathered. Such trials in general represented a crossover design. In many of the crossover trial designs, the time interval between the exposure and data collection of biochemical and biometric outcomes (in blood, urine, and exhaled breath) varied from being contemporaneous (i.e. measures were gathered at the same time as the exposure), to minutes after exposure (e.g. 5, 10, 20, or 30 minutes), up to a 24-hour period after exposure. The remaining trials were in the main laboratory-based studies where assessment of outcomes was made over a consecutive number of days, usually between 3 and 5 days. For a small number of laboratory-based trials, the length of the break time in hours or days between interventions in crossover was not clear. The break time is known as the 'washout' period.

The trials were completed on populations living in 13 countries. The countries were: Belgium (n=5), Canada (n=2), Germany (n=2), Greece (n=7), Hungary (n=1), Indonesia (n=1), Italy (n=13), Japan (n=1), Poland (n=2), South Africa (n=1), Sweden (n=3), Turkey (n=1), the UK (n=10), and the USA (n=37). The trial sample size ranged from 1 to 408. The trials were published between 2010 and 2019.

The number of interventional trial papers grouped under the adapted Academies of Sciences' framework were: 25 under dependence and abuse liability, 21 under cardiovascular diseases, 16 under respiratory diseases, 3 under oral diseases, 13 under exposure to e-cigarette toxins, and 8 under other outcomes. There were no interventional trial papers under the reporting areas of 'cancers', 'developmental and reproductive effects', and 'injuries and poisonings'.

The summary tables for interventional trials are presented under the adapted Academies of Sciences' headings in Sections 4.4.2.1 to 4.4.2.9. These summary tables present details of the authors, study objectives, and the concluding summary finding. For the interventional trials, tables with additional details are presented in Appendix 5.

Table 46 E-cigarette brands, nicotine levels, battery characteristics, and carrier solutions

Characteristics	Details
Brand names	Aspire, American Heritage, Alien 220 box mod, Blu, CE4, Categoria model 401, Categoria model 501, DIPSE, ELIPS C Series, C, eGo, eGo-One, eGo-T, eGo-C 2, eGo XL, Ego-3, Giant, Greensmoke, eVic-VT, CE4 model, Hydro, iStick Pico, Giant, Joyetech, Kanger T2-CC, model Ego, myblu, NPRO, Nobacco, NJOY® King Bold, ONE original, ONEMint, SmokTech, SUR-VAPES, Tornado, TFV8 baby beast tank, V8 Baby-Q2 Core, Vuse Solo, Vype, Vapor King (KR808 model), and White Super.
Nicotine levels	Examples of specific nicotine concentration levels: • 0 mg/mL, 0 mg (placebo), <0.001% nicotine • 1.2%, 1.5 mg/mL, 1.6%, 1.8 % nicotine • 2 mg/mL, 2.4% nicotine, 2.7 mg nicotine/capsule • 3 mg/mL • 11 mg/mL, 12 mg/mL, 14 mg/mL, 16mg/mL, 18 mg/mL • 24 mg/mL, 25 mg/mL, 26 mg/mL, 29 mg/mL • 36 mg/mL • 40 mg/mL, 48 mg/mL Examples of upper threshold levels, means, or nicotine concentration levels: • <10% nicotine • mean 0.6 mg • 0.5–1.8 mg/mL and 12–24 mg/mL A small number of papers reported on how nicotine content was determined. One specific example is: • The authors reported that nicotine was measured by ISO machine-smoking (ISO 3308:2012) and printed on the package, or • The amount of nicotine consumed was calculated by converting the mass of solution consumed into volume by dividing the mass of solution by either the specific density of propylene glycol (1.032 g/cm^3) or of vegetable glycerine (1.261 g/cm^3) or, if the solution was a blend, by estimating it to be a 50:50 ratio and averaging the specific density to 1.147 g/cm^3. The volume was multiplied by the measured nicotine concentration to yield the mass of nicotine consumed during the exposure. The unused e-cigarette cartridges and solutions were collected and sent to the Centers for Disease Control and Prevention for analysis of pH and nicotine concentrations, with analysis performed in a manner that aligned with a published reported methodology.
Battery characteristics	Energy measure • 90 milliampere hour • 350 milliampere hour • 650 milliampere hour • 900 milliampere hour • 1000 milliampere hour • 1100 milliampere hour • 1300 milliampere hour • 3000 milliampere hour • 5000 milliampere hour Voltage • 3.0 volts • 3.3 volts • 3.4 volts • 3.5 volts • 3.7 volts • 4.2 volts Coil resistance • 0.2 ohm • 0.4 ohm • 1.3 ohm • 1.5 ohm

Characteristics	Details	
		1.8 ohm
Carrier solution	•	70.0% propylene glycol and 30.0% vegetable glycerine • 70.8% propylene glycol and 21.2% vegetable glycerine • 72.5% propylene glycol and 18.8% vegetable glycerine • 40.0% propylene glycol and 40.8% vegetable glycerine

4.4.2 Harms, harm reduction, and benefits: e-cigarettes

The harms associated with e-cigarettes identified under the dependence and abuse liability heading and investigated in interventional trials were dependence and higher nicotine uptake than in smokers. The harms identified in e-cigarette users under the cardiovascular diseases heading were increased arterial stiffness and reduced local circulation to the right hand. There were no studies under the cancers heading, but under the exposure to e-cigarette toxins heading, the presence of carcinogens in e-cigarette users was identified. The presence of toxins (metals and volatile organic compounds) was also identified. Three respiratory system harms were identified: reduced vascular function to the lungs, damaged respiratory system organs and tissue, and reduced physiological function. Two harms under the oral diseases heading were identified in e-cigarette users: periodontal disease and increased gingival inflammation when tobacco smokers switched from smoking to vaping. The negative effect of passive nicotine intake through others' vaping was examined in one study.

A number of interventional trials identified that e-cigarettes were less harmful than conventional tobacco cigarettes. For example, some trials reported reduced craving-like sensations in e-cigarette users compared with smokers, and other trials reported lower nicotine uptake in e-cigarette users than in smokers. One trial reported steady progressive improvements in certain exhaled breath measurements and symptom scores when using e-cigarettes compared with smoking conventional tobacco cigarettes. Trials reported that the toxins in tobacco smoke were higher than in e-cigarette vapour.

Two benefits of e-cigarettes were identified in interventional trials. Firstly, e-cigarettes may improve blood flow to the oral mucosa post operatively in non-smoker populations and secondly, smokers who quit smoking by switching to e-cigarettes may limit their post-smoking-cessation weight gain.

4.4.2.1 Dependence and abuse liability: interventional trials

There were 26 papers where participants received an intervention in the form of an e-cigarette and/or e-liquid grouped under dependence and abuse liability (Table 47). The outcomes assessed among e-cigarette users were cravings, desire to smoke, cognitive performance or memory, weight status, and blood or brain nicotine levels. Comparisons of outcomes took account of participants' smoking-related behaviours. This included the difference in outcomes between two or more of the following groups: non-smokers, conventional cigarette smokers, e-cigarette users, and dual users of conventional tobacco cigarettes and e-cigarettes. Comparisons of outcomes also took account of e-cigarette characteristics, including the different pharmacokinetic profiles of conventional tobacco cigarettes and e-cigarettes

Eight trials reported that e-cigarettes reduced craving-like sensations in conventional cigarette users[311-316 317 318] and four trials reported a reduction in the number of cigarettes smoked[314-316 319] By contrast, four trials reported that e-cigarettes did not reduce cravings,[320-323] of which, one trial found that cravings reduced in males but not in females.[323]

One trial reported that former smokers who were daily e-cigarette users transferred their physical dependence to e-cigarettes.[324] Two trials reported that e-cigarettes have potential for abuse liability[325 326] and one trial reported that e-cigarettes maintained a nicotine addiction.[327] Two trials reported that e-cigarettes created dependence and abuse liability among non-users (i.e. those who had never smoked conventional tobacco cigarettes)[328 329] and another trial reported that exposure to e-cigarette use created an urge to smoke or vape among women who smoked conventional tobacco cigarettes.[330]

Two trials reported that e-cigarettes had a positive association with cognitive performance or memory when compared with that of tobacco cigarette users.[313 317]

One trial reported that switching to e-cigarettes may limit their post-cessation weight gain.

Five trials reported that nicotine uptake varied among e-cigarette users. One trial reported brain nicotine uptake level, while the remaining four trials reported blood nicotine level. The findings of the trials were mixed, with two trials reporting that levels of nicotine were lower in e-cigarette users than in tobacco cigarette smokers.[318 331] and three trials reporting equivalent nicotine levels in e-cigarette users and tobacco cigarette smokers.[318 332 333]

Table 47 Interventional trial papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
Eissenberg *et al.* [320] 2010	No benefit	The authors reported on the relationship between **nicotine delivery and craving suppression**, heart rate, and subjective effects. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean: 18.5 cigarettes per day and naïve to e-cigarettes at baseline) using: (1) own brand cigarette (2) sham smoking (puffing an unlit cigarette) (3) e-cigarette 'NPRO' with a 16mg nicotine cartridge (menthol or regular) (4) e-cigarette 'Hydro' with a 16mg nicotine cartridge (menthol or regular) The authors concluded that relative to a tobacco cigarette, 10 puffs from an e-cigarette with a 16 mg nicotine cartridge delivered little to no nicotine and suppressed cravings less effectively. Results on heart rate were not reported.	Non-randomised before and after Latin square trial
Vansickel *et al.* [311] 2010	Benefit	The authors reported on the relationship between own-brand **cigarettes, two types of e-cigarette devices,** and a sham (unlit cigarette) with **plasma nicotine and carbon monoxide (CO) concentrations**, heart rate, and a range of subjective effects. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean: 22 cigarettes per day at baseline) using: (1) own brand cigarette (2) sham smoking (3) 'NPRO' e-cigarette with a 18mg nicotine cartridge (menthol or regular) (4) 'Hydro' e-cigarette with a 16mg nicotine cartridge (menthol or regular). The authors concluded that in acute testing conditions, neither of the e-cigarettes exposed users to measurable levels of nicotine or CO, although both suppressed nicotine/tobacco abstinence symptom ratings.	Non-randomised before and after Latin square trial
Dawkins *et al.* [323] 2012	Benefit for men	The authors reported on the relationship between **e-cigarettes and effects on desire to smoke, withdrawal symptoms, and cognition**. The study aimed to explore whether e-cigarettes can reduce desire to smoke and also reduce abstinence-related withdrawal symptoms over a 20-minute period. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (naïve to e-cigarettes at baseline) using: (1) 18mg nicotine 'Super While' e-cigarette (2) 0mg nicotine 'Super While' e-cigarette (3) just hold 'Super While' e-cigarette	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		The authors concluded that desire to smoke and some aspects of nicotine withdrawal were significantly reduced 20 (but not 5) minutes after e-cigarette use; in this respect, the nicotine e-cigarette was superior to placebo in males but not in females. Nicotine derived via use of e-cigarettes also improved working memory performance, particularly at the longer interference intervals.	
Vansickel *et al.*[312] 2012	Benefit compared with combustible tobacco cigarettes	The authors assessed the **abuse liability of e-cigarettes**. *Comparative groups* Conventional combustible tobacco cigarette users - comparison(s) (≥20 cigarettes per day at baseline) using: (1) e-cigarette users taking bouts of 'Vapour king'. separated by 30 minutes (2) e-cigarette users taking bouts of 'Vapour king'. Own brand tobacco cigarettes 10 puffs and varying amounts of money (3) e-cigarette users taking bouts of 'Vapour king'. Tobacco cigarettes 10 puffs and a varying number of own brand cigarette (4) e-cigarette users taking 1-10 own brand puffs and varying amounts of money using the multiple-choice procedure The authors concluded that e-cigarettes can deliver clinically significant amounts of nicotine and reduce cigarette abstinence symptoms. In addition, they appear to have lower potential for abuse relative to traditional tobacco cigarettes.	Group randomised controlled trial
Dawkins *et al.*[313] 2013	Benefit	The authors reported on the relationship between nicotine derived from e-cigarettes and time-based prospective memory in abstinent smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoked within 1 hour of waking and ≥10 cigarettes per day for ≥ 1 year at baseline) using: (1) Super While' nicotine 18mg tobacco flavoured (2) Super While' nicotine 0mg tobacco flavoured The authors concluded that **compared with placebo, nicotine e-cigarettes reduced the desire to smoke and tobacco withdrawal symptoms**, and improved time-based but not event-based prospective memory. There was a moderate, marginally significant negative correlation between prospective memory performance during abstinence and nicotine dependence.	Non-randomised crossover trial
Adriaens *et al.*[314] 2014	Benefit	The authors reported on the effectiveness of **e-cigarettes** in an 8-week Flemish study with 6-month follow-up on **smoking reduction, craving, and experienced benefits and complaints**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users using: (1) 'Joyetech eGo-C' supplied with 30mL bottles of tobacco-flavour e-liquid (Dekang 'Turkish Blend') containing 18mg/mL of nicotine (2) 'Kanger T2-CC' supplied with 30mL bottles of tobacco-flavour e-liquid (Dekang 'Turkish Blend') containing 18mg/mL of nicotine The authors concluded that in a series of controlled laboratory sessions with e-cigarette-naive tobacco smokers, second-generation e-cigarettes were shown to be immediately and highly effective in reducing abstinence-induced cigarette craving and withdrawal symptoms, while not resulting in increases in exhaled	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		carbon monoxide. Remarkable (>50%) 8-month reductions in, or complete abstinence from, tobacco smoking was achieved with e-cigarettes in almost half (44%) of the participants.	
Nides *et al.* [315] 2014	Benefit	The authors reported on the relationship between short-term **smoking reduction with an electronic nicotine delivery system** and **nicotine blood levels, heart rate, and cravings**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥10 cigarettes per day for ≥ 1 year at baseline) with: (1) e-cigarette users using disposable NJOY King Bold device with a wad containing 0.5mL of nicotine solution, e-liquid nicotine solution with approximately 25 mg of nicotine and menthol flavoured The authors concluded that the NJOY® King Bold e-cigarette delivered nicotine and led to short-term smoking reduction.	Non-randomised before and after study
Polosa *et al.* [316] 2014b	Benefit	The authors examined the effect of **e-cigarettes as an aid for smokers to quit or reduce cigarette consumption**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥15 cigarettes per day for ≥ 10 years at baseline) with: (1) e-cigarette device 'Categoria' with nicotine cartridges The authors concluded that long-term e-cigarette use can substantially decrease cigarette consumption in smokers not willing to quit; in addition, it is well tolerated.	Non-randomised before and after study
Polosa *et al.* [319] 2014c	Benefit	The authors reported on success rates with **nicotine personal vaporisers in a prospective 6-month pilot study of smokers not intending to quit**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥15 cigarettes per day for ≥ 10 years at baseline) with: (1) e-cigarette device 'EGO/CE4' with e-liquid containing nicotine 9mg/ml The authors concluded that the use of second-generation personal vaporisers substantially decreased cigarette consumption without causing significant adverse effects in smokers not intending to quit; in addition, participants' perception and acceptance of the products was very good.	Non-randomised before and after study
Russo *et al.*[334] 2016	Benefit	The authors reported on the relationship **between e-cigarettes and weight gain.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥15 cigarettes per day for ≥ 10 years at baseline) with: (1) e-cigarette users using 'Categoria' 'Original 2.4%', (2) e-cigarette users using 'Categoria' 'Original 1.8%' (3) e-cigarette users using 'Categoria' 'Original 0%'. The authors concluded that smokers who quit smoking by switching to e-cigarettes may limit their post-cessation weight gain, with substantial reversal in weight gain manifesting at later timepoints.	Randomised controlled trial
Caponnetto *et al.* [317] 2017	Benefit	The authors reported on **cognitive performance, craving, and gesture (physical act of having a conventional combustible tobacco cigarette in hand) in subjects using e-cigarettes and their usual cigarettes**. *Comparative groups*	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		Comparison(s) of conventional combustible tobacco cigarette users (≥15 cigarettes per day for ≥ 10 years at baseline) using: (1) first generation rechargeable cigalike e-cigarette with 24mg nicotine and tobacco aroma (2) second generation disposable cigalike e-cigarette with 0mg nicotine mint aroma (3) second generation personal vaporizer model Ego C with liquid nicotine 24mg tobacco aroma, and (4) usual conventional combustible tobacco cigarette The authors concluded that the cognitive measures of attention, executive function, and working memory are not influenced by different e-cigarettes and sex, demonstrating that in general, e-cigarettes could become a strong support from a cognitive point of view for those who decide to quit smoking. It seems that not only cravings and other smoking withdrawal symptoms, but also cognitive performance, are linked to the presence of nicotine; this suggests that the reasons behind the dependence and the related difficulty in quitting smoking needs to be examined. The physical act of smoking conventional combustible tobacco cigarettes also needs to be studied.	
Hiler *et al*. [335] 2017	Harm	The authors looked at the relationship between nicotine delivery profile and cardiovascular and subjective effects. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥10 cigarettes per day and e-cigarette naive at baseline) with: (1) 'eGo' e-cigarette 0 mg/ml nicotine (2) 'eGo' e-cigarette 8 mg/ml nicotine, (3) 'eGo' e-cigarette 18 mg/ml nicotine (4) 'eGo' e-cigarette 36 mg/ml nicotine E-cigarette users themselves (≥ 3 months use with ≥ 1 ml of e-cigarette solution daily containing nicotine concentration ≥ 8 mg/ml and using ≤ 5 conventional tobacco cigarettes daily at baseline) with the same 4 interventions listed above. The authors concluded that participants' plasma nicotine concentration was related directly to liquid nicotine concentration and was dependent on user experience, with significantly higher mean plasma nicotine increases observed in e-cigarette-experienced individuals relative to e-cigarette-naive smokers in each active nicotine condition.	Randomised crossover or Latin-square trial
Stiles *et al.* [331] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors evaluated the **abuse liability of three Vuse Solo e-cigarettes** with a nicotine content ranging from 14 mg cartridge, to 29mg, and to 36 mg, relative to high- and low-abuse liability comparator products (usual brand combustible cigarettes and nicotine gum, respectively). *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥10 king size filtered cigarettes per day for ≥ 6 months and e-cigarette and first cigarette within 30 minutes of waking at baseline) with: (1) e-cigarette device Vuse Solo (2) nicotine gum Participants could also use their own cigarette during the study The authors concluded that the use of Vuse Solo e-cigarettes resulted in subjective measures (product liking, intent to use product again, product effects, urge to smoke, and urge for product) and nicotine uptake	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		that were between those of combustible cigarettes and nicotine gum, although generally closer to nicotine gum. Compared with combustible cigarettes, use of Vuse Solo e-cigarettes resulted in significantly lower scores in measures of product liking, positive effects, and intent to use again. These pharmacodynamic findings were consistent with the pharmacokinetic data, showing that tobacco cigarettes produced substantially faster and higher levels of nicotine uptake when compared with Vuse Solo e-cigarettes and nicotine gum. Vuse Solo e-cigarettes resulted in more rapid initial uptake of nicotine compared to nicotine gum, but peak concentration and long-term extent of uptake were not different or were lower with Vuse Solo e-cigarettes. Collectively**, these findings suggest that Vuse Solo cigarettes likely have an abuse liability that is somewhat greater than nicotine gum but lower than cigarettes.**	
Adriaens *et al*. [1] 2018	No benefit	Authors reported on a three-day randomised crossover trial, focusing on the **behavioural and experiential effects of the short-term use of the heat-not-burn product IQOS™**, versus an e-cigarette, and versus a regular cigarette, in current smokers who were novice users for both IQOS™ and e-cigarettes. To investigate the effect of using an IQOS™ on exhaled carbon monoxide, **acute cigarette craving, withdrawal symptoms, and subjective positive and negative experiences** after overnight smoking abstinence, compared to using an e-cigarette or a regular tobacco cigarette. And to investigate which product (e-cigarette or IQOS™) would be preferred. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥10 cigarettes per day for ≥ 3 years at baseline) with: (1) own habitual regular brand of cigarettes (2) Eleaf iStick e-cigarette with 18mg/mL nicotine with either a tobacco or menthol flavour (3) IQOS heat-not-burn tobacco product The authors concluded that short-term use of a specific heat-not-burn product, IQOSTM, can be effective to momentarily reduce acute cigarette craving and withdrawal symptoms, while having a minimal impact on the exhaled carbon monoxide levels, and being slightly more liked by novice users than an e-cigarette. They stated however that this does not guarantee that craving/withdrawal symptom reduction will also be sustained over longer time spans or in case of repeated use, nor do they provide assurance that these effects are sufficient to lead to smoking reduction or cessation in smokers willing to quit or cut down on cigarettes.	Non-randomised crossover trial
Baldassarri *et al.* [326] 2018	Harm	The authors examined the relationship between **e-cigarette use and Beta2*-nicotinic acetylcholine receptors** (β2*-nAChR) occupancy. Comparative groups E-cigarette users themselves (for ≥ 1 month at baseline) with (1) 0 mg/ml e-cigarette (2) 8 mg/ml e-cigarette (3) 36 mg/ml EC e-cigarette (4) tobacco cigarette	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		Comparison(s) of conventional combustible tobacco cigarette users (≥11 cigarettes per day for ≥1 year and e-cigarette and first cigarette within 30 minutes of waking at baseline) with same four products The authors concluded that the e-cigarettes studied have abuse liability and may provide an adequate alternative nicotine delivery system for cigarette smokers.	
Hobkirk *et al.* [332] 2018	Harm	The authors reported on **changes in resting state functional brain connectivity and withdrawal symptoms associated with acute e-cigarette use.** *Comparative groups* Comparison(s) of e-cigarette users themselves (≥20 days out of the last 28 days with a nicotine concentration of ≥12mg/mL at baseline) with: (1) their own e-cigarette after 14 hours of nicotine abstinence The authors concluded that the preliminary results suggest that the effects of e-cigarette use on resting state functional brain connectivity are like those seen with nicotine administration in other forms.	Non-randomised before and after study
Ruther *et al.* [327] 2018	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **nicotine delivery efficiency of first- and second-generation e-cigarettes** and their impact on relief of cravings during the acute phase of use. *Comparative groups* Comparison(s) of e-cigarette users themselves (regular users of nicotine-containing e-cigarettes for ≥ 3months and not smoked for ≥1 month at baseline) with: (1) Cigalike American Heritiage 18.0 mg/mL nicotine content, (2) Cigalike Vype 18.6 mg/mL nicotine content, (3) Blu 18.0 mg/mL nicotine content (4) Tank model Aspire/Joytech Upgrade Set 18.0 mg/mL nicotine content (5) conventional tobacco cigarette Marlboro Red 0.8mg nicotine per cigarette Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 5 cigarettes per day for ≥ 3 years at baseline) with the same five products: The authors concluded that the heart rate of tank mode users was markedly lower than that of the tobacco cigarette users. Unlike disposable cigalikes, tank mode e-cigarettes represent an effective source of nicotine and might be used as an alternative nicotine replacement product to aid smoking cessation. However, nicotine plasma levels observed in tank mode users after short-term vaping also have the potential to produce and sustain nicotine addiction.	Non-randomised crossover trial
Cobb *et al.* [328] 2019	Harm	The authors reported on the **influence of e-cigarette liquid flavours and nicotine concentration on subjective measures of abuse liability** in young adult e-cigarette vapers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked mean of 10.1 cigarettes per day for a mean of 18.3 months at baseline) using: (1) own brand cigarette (2) e-cigarette combinations 1 ml of one of three liquid flavours (Food/Dessert/Spice) 0mg/ml nicotine concentration. (3) fruit 0mg/ml nicotine concentration. (4) tobacco/Menthol at either 0mg/ml nicotine concentration (5) e-cigarette combinations 1 ml of one of three liquid flavours (Food/Dessert/Spice) 36 mg/ml nicotine concentration	Non-randomised Latin square trial.

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		(6) fruit 36 mg/ml nicotine concentration (7) tobacco/Menthol at either 36 mg/ml nicotine concentration The authors concluded that among young adult vapers, e-cigarette containing nicotine were positively associated with several, but not all, subjective measures of abuse liability. Flavours did not consistently mask/enhance the effects observed. The results reinforce continued examination of e-cigarette-delivered nicotine and liquid flavours in relation to abuse liability.	
De La Garza *et al.* [321] 2019	Harm	The authors reported on **e-cigarette-naive cigarette smokers and the effects on cravings** after acute exposure to e-cigarettes in the laboratory. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 11 cigarettes per day for 1 years and were e-cigarette naïve at baseline) using: (1) participant's own brand conventional tobacco cigarette (2) eGO with e-liquid Virginia Pure tobacco flavoured containing 0 mg/ml of nicotine (3) eGO with e-liquid Virginia Pure tobacco flavoured containing 18mg/ml nicotine (4) eGO with e-liquid Virginia Pure tobacco flavoured containing 36 mg/ml of nicotine The authors concluded that e-cigarettes did not reduce cravings or smoking severity in e-cigarette-naive smokers.	Randomised crossover trial
Hughes *et al.* [324] 2019a	Harm	The authors reported on the **symptoms of nicotine withdrawal in former smokers who were current daily e-cigarette users.** *Comparative groups* Comparison(s) of e-cigarette users themselves (daily for ≥ 2 months and using refillable tank, but not a JUUL. Former smoker for ≥1 year, and ≤6 tobacco cigarettes in the last year at baseline) with: (1) participants own e-cigarette. The authors concluded that former smokers who are daily e-cigarette users transfer physical dependence on tobacco cigarettes to dependence on e-cigarettes. The severity of withdrawal from e-cigarettes appears to be only somewhat less than that from daily tobacco cigarette use.	Non-randomised before and after study
Hughes *et al.* [329] 2019b	Harm	The authors reported on **withdrawal symptoms from e-cigarette abstinence among adult never-smokers.** *Comparative groups* Comparison(s) of e-cigarette users themselves who were never smokers (daily at baseline) with: (1) participants own nicotine containing e-cigarette The authors concluded that withdrawal symptoms can occur in never-smokers who are daily e-cigarette users. However, the severity of withdrawal from e-cigarette abstinence in never-smokers appears to be small and may not be of clinical or regulatory significance.	Non-randomised before and after study
Maloney *et al.* [325] 2019	More harm than nicotine replacement therapy Less harmful than conventional	The authors conducted an **abuse liability assessment of an e-cigarette use in combustible cigarette smokers.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 10 cigarettes per day for ≥1 year at baseline) using: (1) participants own brand cigarette (2) e-cigarette with nicotine 36mg (3) e-cigarette with no nicotine	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
	combustible tobacco cigarettes	(4) Food and Drug Administration nicotine inhaler The authors concluded that the abuse liability of the e-cigarette examined was higher than the Food and Drug Administration-approved nicotine inhaler but lower than combustible cigarettes.	
O'Connell *et al.* [318] 2019	Benefit	The authors evaluated the **pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations** in adult smokers in the USA. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 10 cigarettes per day for ≥1 year at baseline) using: (1) myblu pod-system containing 25mg nicotine ('freebase') tobacco flavour (2) myblu pod-system containing 16 mg nicotine lactate tobacco flavour (3) myblu pod-system containing 25mg nicotine lactate tobacco flavour (4) myblu pod-system containing 40 mg lactate tobacco flavour (5) blu PRO open system containing 48 mg nicotine lactate tobacco flavour (6) own brand commercially available conventional tobacco cigarettes The authors concluded that the rate of nicotine absorption into the bloodstream was comparable among all e-cigarettes tested and was as rapid as that for conventional combustible tobacco cigarettes. However, in all cases, nicotine delivery did not exceed that of the conventional combustible tobacco cigarette. The pharmacokinetic profiles of nicotine salt emissions were also dependent upon the properties of the e-cigarette device. Subjective scores were numerically highest after smoking a conventional combustible tobacco cigarette, followed by the Myblu 40 mg nicotine salt formulation per cigarette. The rise in nicotine blood levels following use of all tested e-cigarettes was quantified as 'a little' to 'modestly' satisfying in terms of relieving the desire to smoke. All products were well tolerated with no notable adverse events reported. These results demonstrate that, while delivering less nicotine than a conventional combustible tobacco cigarette, the use of nicotine salts in e-cigarettes enables cigarette-like pulmonary delivery of nicotine that reduces the desire to smoke.	Randomised crossover trial
Solingapuram Sai *et al.*[333] 2019	Both benefit and harm	The authors reported on the **relationship between e-cigarettes and brain nicotine kinetics.** *Comparative groups* Comparison(s) of e-cigarette users themselves who were never smokers (exclusive, current users ≥ 4 times per month) and e-cigarette users (current ≥ 4 times per month at baseline) who were former smokers (with a mean of 21 years smoking): (1) standardised puff of vapour from V2 Rede-liquid 1.2% nicotine (2) conventional combustible tobacco cigarette a shortened Basic Gold 100's cigarette (Philip Morris) The authors concluded that e-cigarettes can deliver nicotine to the brain with similar rapidity as conventional tobacco cigarettes. Therefore, to the extent that rapid brain uptake promotes smoking reward, e-cigarettes might maintain a degree of nicotine	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		dependence and also serve as non-combustible substitutes for cigarettes.	
St. Helen *et al.*[322] 2019	Equally harmful	The authors reported on the **relationship between e-cigarettes and nicotine exposure in dual users of e-cigarettes and conventional combustible tobacco cigarettes.** *Comparative groups* Comparison(s) of dual users (conventional combustible tobacco cigarette users who smoked ≥5 cigarettes per day and e-cigarette users who used the same device ≥1 time per day in the past month at baseline) with: (1) participants used their usual brand of conventional tobacco cigarette users (2) Cig-alike e-cigarette (3) pod type e-cigarette, (4) fixed-power e-cigarette (5) variable-power e-cigarette tank devices. The authors were not able to detect any differences in withdrawal symptoms, affective states, and urge to smoke cigarettes between e-cigarette and dual users of e-cigarettes and conventional combustible tobacco cigarettes.	Non-randomised crossover trial
Vena *et al.*[330] 2020	Harm	The authors reported on the **relationship between passive exposure to the use of a female-marketed e-cigarette with selectively enhanced smoking urge, cigarette and e-cigarette desire**, and smoking behaviour among women (versus men) smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette (who smoked ≥ 5 cigarettes per day and were not attempting to quit at baseline) with: (1) hot-pink coloured iStick Pico e-cigarette mod device adorned with a jewelled crown or bow charm (VaporDolls, Etsy) The authors concluded that both women and men were sensitive to the use of the female-marketed e-cigarettes as a smoking cue.	Non-randomised before and after study

4.4.2.2 Cardiovascular diseases: interventional trials

There were 21 interventional trial papers examining the relationship between e-cigarettes and cardiovascular diseases (Table 48).

The measures assessed in order to evaluate cardiovascular health included:

- Blood counts
- Myocardial function
- Arterial stiffness and arterial pressure
- Systolic and diastolic blood pressure and heart rate
- Endothelial progenitor cells
- Vagal and sympathetic activity
- Microvascular endothelial function and oxidative stress
- Vascular and haemodynamic measures (cardio-ankle vascular index, flow-mediated dilation), and
- Oxidative stress levels.

One 21-day crossover trial examined the relationship between e-cigarettes and blood count measures, gauging 15 markers at three timepoints in the first week, followed by a 1-week break, known as a washout period, before the process was repeated with conventional tobacco cigarettes in the third week.[336] The authors concluded that the results suggest that active e-cigarette smoking in smokers and passive e-cigarette smoking in never-smokers did not affect markers of complete blood count. By contrast, active tobacco cigarette smoking in smokers and passive tobacco cigarette smoking in never-smokers increased white blood cell count, lymphocyte count, and granulocyte count for at least 1 hour.

One trial assessed 11 markers of myocardial function following 7 minutes of e-cigarette use.[337] The authors stated that e-cigarette use had no immediate effect on myocardial function.

Four trials examined the effects of e-cigarettes on arterial stiffness. One trial reported no effect on arterial stiffness following 15 puffs of an e-cigarette during the intervention,[338] while a second trial reported unfavourable effects on aortic stiffness in 20 participants after 30 minutes of e-cigarette use.[339] A third trial examined the differential effects of e-cigarette carrier solvents (propylene glycol and glycerol) and of nicotine on micro- and macrovascular function, including arterial stiffness in an 11-day crossover trial.[340] The authors reported that the increased indices of arterial stiffness (harmful) were attributable to nicotine but not to other components in the vaporised inhalant. The fourth trial reported on the relationship between e-cigarette smoking and increases in aortic stiffness and blood pressure in young smokers and concluded that various patterns of e-cigarette smoking clearly demonstrated an unfavourable effect on aortic stiffness and blood pressure.[341] The authors reported that using e-cigarettes for 30 minutes induces an unfavourable effect on aortic stiffness similar to tobacco cigarette smoking. The influence of e-cigarette smoking at 5 minutes on aortic stiffness is not as prompt (peak effect at 15 minutes) and is less potent compared with the effect of tobacco cigarette smoking.

Four trials examined a combination of oxidative stress and vascular function. Three reported harms related to e-cigarettes and the fourth reported no harm. The first short-term crossover trial examined the acute impact of tobacco and e-cigarette smoking on oxidative stress and vascular function and concluded that smoking both e-cigarettes and conventional tobacco cigarettes led to a significant increase in the levels of soluble NOX2-derived peptide and 8-iso-prostaglandin F2α and a significant decrease in nitric oxide bioavailability, vitamin E levels, and flow mediated dilation 30 minutes after intervention.[342] The second trial examined the role of nicotine versus non-nicotine constituents in e-cigarette emissions in causing increased resting cardiac sympathetic nerve activity and increased susceptibility to oxidative stress in otherwise healthy humans.[343] The authors concluded that the

acute sympathomimetic effect of e-cigarettes (measured 10 minutes after exposure) is attributable to the inhaled nicotine, not to non-nicotine constituents in e-cigarette aerosol, reproducing the same heart rate variability pattern associated with increased cardiac risk in multiple populations with and without known cardiac disease. However, evidence of oxidative stress, as estimated by plasma paraoxonase activity, was not uncovered following acute e-cigarette exposure. The third study, a short-term crossover trial, examined the relationship of conventional tobacco cigarettes and e-cigarettes with oxidative stress and endothelial dysfunction and reported that absolute changes in oxidative stress and vascular features immediately after smoking a conventional cigarette and vaping an e-cigarette were significantly associated with oxidative stress and endothelial dysfunction, with one exception of 8-iso-prostaglandin F2α-III levels.[344] One three-period 21-day crossover trial reported on the differential effects of e-cigarettes (specifically the differential effects of vehicles, propylene glycol and glycerol, and nicotine) on macro and microvascular function, arterial stiffness, and oxidative stress.[345] The authors concluded that high-temperature e-cigarette vehicle vaporisation does not alter micro- and macrovascular function or oxidative stress at 15 and 30 minutes after vaping, and that these effects are solely attributable to nicotine. Since our mapping exercise another prospective study, with a non-randomised trial and cohort study combined, reported that conventional tobacco cigarette smokers, particularly females, demonstrate significant improvement in vascular health within 1 month of switching from a tobacco cigarette to an electronic cigarette.[346]

One crossover trial reported on the relationship between e-cigarettes and an increase in the number of endothelial progenitor cells in the blood of healthy volunteers.[347] The authors concluded that in healthy volunteers, 10 puffs of e-cigarette vapour inhalation caused an increase in endothelial progenitor cells up to 24 hours following use. This increase was of the same magnitude as that following smoking one conventional cigarette. Taken together, these results may represent signs of possible vascular changes after short e-cigarette inhalation.

Six trials reported on the relationship between e-cigarettes and heart rate and/or blood pressure. Two trials reported no effect and four trials reported a harmful effect. The first trial was an RCT and reported on the effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to e-cigarettes over a 1-year period and concluded that quitting smoking with the use of e-cigarettes does not lead to higher blood pressure values.[348] The second trial reported on the effects of e-cigarette use on vascular measures of health up to 2 hours after exposure and concluded that there were no significant changes in heart rate, systolic and diastolic blood pressure, endothelial function, or arterial stiffness throughout the experiment.[349] By contrast, the third trial (a crossover trial) reported on the relationship of e-cigarettes and cigarettes with peripheral and central haemodynamics, as well as arterial stiffness measured for up to 2 hours after exposure and concluded that there were increases in peripheral and central blood pressure and also in pulse wave velocity after either smoking a conventional cigarette or after vaping a nicotine-containing e-cigarette.[350] The fourth trial investigated the effects of the e-cigarette liquid solvents propylene glycol and vegetable glycerine on user nicotine delivery, heart rate, subjective effects, and puff topography over 12 days; the authors concluded that participants' heart rates increased significantly after e-cigarette use.[351] The fifth trial, a crossover 5-day trial, examined the exercise-induced heart rate response and heart rate variability in subjects caused by inhaling smoke from conventional tobacco cigarettes and aerosolised vapour from e-cigarettes and concluded that a significant acute autonomic cardiac modulation during exercise is induced by an acute episode of using either conventional tobacco cigarettes or e-cigarettes.[352] The sixth trial consisted of two RCTs separated by at least 1 week and tested a placebo e-cigarette and 18 mg per ml nicotine e-cigarette and reported on the acute cardiorespiratory and performance effects of vaporised nicotine delivered via e-cigarettes at rest and during cycle exercise in young, normotensive, non-smoking subjects.[353] The authors concluded that acute vaporised nicotine inhalation via e-cigarettes increases resting and exercise diastolic blood pressure but does not affect resting metabolic rate or cycle aerobic power.

One trial reported on the impact of conventional cigarette versus e-cigarette smoking on platelet function.[354] Each participant smoked a conventional cigarette then returned 1 week later to vape a study e-cigarette with the same nominal nicotine content. Blood samples were drawn shortly before and 5 minutes after each episode. The authors concluded both conventional cigarette and e-

cigarettes have short-term effects on platelet activation, although in non-smokers the use of e-cigarettes had a less important impact on platelet function.

Two papers examined the relationship between e-cigarettes and cardio-respiratory function. One three-period 21 day crossover trial reported on the acute effects of vaping and their reversibility on biological/clinical cardio-respiratory parameters and concluded that short-term e-cigarette cessation by regular users decreases baseline heart rate and lung inflammation and increases forced expiratory flow by 25%, suggesting that high-wattage vaping alters airway function.[355] In addition, acute nicotine vaping increased systolic blood pressure, diastolic blood pressure, and heart rate.[355] The second trial, a three-period crossover trial, which was investigator-blinded and conducted over 21 days with former smokers who were exclusive nicotine e-cigarette users for a least 1 year at baseline, concluded that short-term e-cigarette cessation by regular users decreases baseline heart rate and lung inflammation and increases forced expiratory flow, suggesting that vaping negatively alters airway function.[356]

One paper concluded that a 24 mg e-cigarette significantly reduced vapers' hand microcirculation during and up to 20 minutes post intervention.[357]

Table 48 Interventional trial papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
Flouris *et al.*[336] 2012	No harm identified	The authors investigated the **acute effects of electronic and tobacco cigarette smoking on complete blood count.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 15 cigarettes per day and were e-cigarette naive at baseline) with: (1) control session (ASCON), (2) an active tobacco cigarette smoking session (ASTOB) (3) an active e-cigarette smoking session (ASE-CIG) Comparison(s) of never conventional combustible tobacco cigarette and never e-cigarette users at baseline) with the same 3 interventions. The authors concluded that active e-cigarette smoking in smokers and passive e-cigarette smoking in never-smokers do not affect markers of complete blood count. By contrast, active tobacco cigarette smoking in smokers and passive tobacco cigarette smoking in never-smokers increase white blood cell count, lymphocyte count, and granulocyte count for at least 1 hour.	Randomised crossover trial
Farsalinos *et al.*[337] 2014b	No harm identified	The authors reported on **the acute effects of using an e-cigarette on myocardial function.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 15 cigarettes per day for ≥5 years at baseline) with Electronic cigarette users who were former smokers (daily, 9-12 mg/ml nicotine-containing liquid for ≥1 month) after both received: (1) one commercially available conventional combustible tobacco cigarette of the same nicotine (1.0 mg), tar (10 mg) and carbon monoxide (10 mg) yields. The authors concluded that although acute smoking causes a delay in myocardial relaxation, e-cigarette use has no immediate effects. E-cigarettes' role in tobacco harm reduction should be studied intensively in order to determine whether switching to e-cigarette use may have long-term beneficial effects on smokers' health.	Non-randomised before and after study
Szoltysek *et al.*[338] 2014	No harm identified	The authors reported on the **influence of inhaled nicotine from conventional combustible tobacco cigarettes versus e-cigarettes on arterial stiffness.** *Comparative groups*	Non-randomised

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		Comparison(s) of e-cigarette users themselves who were former smokers (current users of with nicotine-containing liquid for ≥1 month at baseline) with conventional combustible tobacco cigarette users smoking ≥15 cigarettes per day for ≥5 years at baseline) after both received: (1) second-generation device eGo-T battery with liquid containing 11 mg/ml nicotine concentration The authors concluded that in contrast to conventional combustible tobacco cigarette use, the use of e-cigarettes causes no changes in arterial stiffness. They suggested that this may indicate lower bioavailability of nicotine from the e-cigarette or an additional effect of other substances present in cigarette smoke but absent in an e-cigarette aerosol.	crossover trial
Cooke *et al.* [339] 2015	Harm	The authors reported on the **effect of acute inhalation of vaporised nicotine on arterial pressure** in young non-smokers. *Comparative groups* Comparison(s) of non-conventional combustible tobacco cigarette users (never smokers at baseline) with: (1) e-cigarette containing nicotine (18 mg) (2) a placebo (0 mg nicotine) The authors concluded that vaporised nicotine inhalation is not harmless.	Randomised crossover trial
Yan *et al.* [340] 2015	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **effects of using e-cigarettes on nicotine delivery and cardiovascular function** in comparison with conventional combustible tobacco cigarettes. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked mean of 10 cigarettes per day for ≥ 1 year at baseline) using: (1) blu e-cigs commercial products (Product D) that contain 16 mg/mL (1.6%) nicotine and (2) blu e-cigs commercial products (Product E) that contain 16 mg/mL (1.6%) nicotine and (3) non-commercial products (Product A) that contain 24 mg/mL (2.4%) nicotine (4) non-commercial products (Product B) that contain 24 mg/mL (2.4%) nicotine (5) non-commercial products (Product C) that contain 24 mg/mL (2.4%) nicotine (6) the market-leading conventional cigarette (Marlboro) with approximately 0.8 mg nicotine per cigarette (FTC 2007). The authors concluded that the nicotine plasma concentrations after 1.5 hours of e-cigarette product use were significantly lower in the users of e-cigarettes than in users of Marlboro cigarettes. The combination of glycerine and propylene glycol as the delivery vehicle facilitated delivery of more nicotine than the use of glycerine alone. Heart rate and systolic and diastolic blood pressure, were significantly elevated after use of Marlboro cigarettes, but the elevation was less after use of most of the e-cigarettes tested. Use of e-cigarettes had no impact on exhaled carbon monoxide levels, whereas the Marlboro cigarettes significantly increased exhaled carbon monoxide to more than eight times above the baseline.	Randomised crossover trial
Antoniewicz *et al.* [347]	Harm	The authors reported on the relationship between **e-cigarettes and an increase in the number of endothelial progenitor cells** in the blood of healthy volunteers. *Comparative groups*	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
2016		Comparison(s) of conventional combustible tobacco cigarette users (who smoked maximum 10 cigarettes per month at baseline) with: (1) second-generation electronic cigarette device (eGo XL) and an e-liquid with nicotine 12 mg/ml The authors concluded that in healthy volunteers, 10 puffs of e-cigarette vapour inhalation caused an increase in endothelial progenitor cells. This increase was of the same magnitude as that following smoking one conventional combustible tobacco cigarette. Taken together, these results may represent signs of possible vascular changes after short e-cigarette inhalation.	
Carnevale *et al.* [342] 2016	Harm	The authors examined the **acute impact of tobacco and e-cigarette smoking on oxidative stress and vascular function.** Indicators of oxidative stress (serum levels of soluble NADPH oxidase 2 (NOX2)-derived peptide, nitric oxide bioavailability, 8-iso-prostaglandin F2α-III, and vitamin E) and endothelial dysfunction (flow-mediated dilation) were collected. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked a mean of 11.1 cigarettes per day for a mean of 6.4 years at baseline) with: (1) conventional combustible tobacco cigarette with mean nicotine content of 0.6 mg (2) tobacco-flavoured e-cigarette with a nicotine content of 16mg per cartridge The authors concluded that smoking both e-cigarettes and conventional combustible tobacco cigarettes led to a significant increase in the levels of soluble NOX2-derived peptide and 8-iso-prostaglandin F2α and a significant decrease in nitric oxide bioavailability, vitamin E levels, and flow mediated dilation.	Non-randomised crossover trial
Farsalinos *et al.* [348] 2016	No harm identified	The authors reported on the effect of **continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to e-cigarettes.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked ≥ 5 cigarettes per day for ≥ 5 years and not intending to quit at baseline) with: (1) 'Original' 2.4% nicotine Categoria'; Arbi Group Srl, Italy (2) Categoria'1.8 % nicotine Categoria'; Arbi Group Srl, Italy (3) Original' without nicotine and with 'sweat tobacco' aroma Categoria'; Arbi Group Srl, Italy The authors concluded that quitting smoking with the use of e-cigarettes does not lead to higher blood pressure values, and this is independently observed whether e-cigarettes are regularly used or not.	Randomised controlled trial
Fogt *et al.* [353] 2016	Harm	The authors reported on the **acute cardiorespiratory and performance effects of vaporised nicotine delivered via e-cigarettes at rest and during cycle exercise** in young, normotensive, non-smoking subjects. *Comparative groups* Comparison(s) of non-smokers (conventional combustible tobacco cigarette) using: (1) e-cigarettes placebo (0 mg nicotine) (2) e-cigarettes types nicotine (18 mg nicotine) The authors concluded that acute vaporised nicotine inhalation via e-cigarettes increases resting and exercise diastolic blood pressure but does not affect resting	Two randomised controlled trials

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		metabolic rate or cycle aerobic power in young, normotensive non-smokers.	
Vlachopoulos *et al.* [341] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **e-cigarette smoking and increases in aortic stiffness and blood pressure** in young smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users using: (1) conventional combustible tobacco cigarette (2) e-cigarette over a 5-minute period (3) e-cigarette over a 30-minute period (4) nothing (a sham) The authors concluded that various patterns of e-cigarette smoking on aortic stiffness and blood pressure clearly demonstrated an unfavourable effect. Using e-cigarettes for 30 minutes induces an unfavourable effect on aortic stiffness similar to tobacco cigarette smoking. The influence of e-cigarette smoking for 5 minutes on aortic stiffness is not as prompt (peak effect at 15 minutes) and is less potent compared with the effect of tobacco cigarette smoking.	Non-randomised before and after study
Moheimani *et al.* [343] 2017	Harm	The authors reported on the role of **nicotine versus non-nicotine constituents in e-cigarette emissions in causing increased resting cardiac sympathetic nerve activity and increased susceptibility to oxidative stress** in otherwise healthy humans. *Comparative groups* Comparison(s) of not current conventional combustible tobacco cigarette or e-cigarette users (but could be former users for >1 year at baseline) using: (1) e-cigarette the Greensmoke cigalike device with tobacco-flavoured liquid and 1.2% nicotine (2) e-cigarette the Greensmoke cigalike device with tobacco-flavoured liquid and 0% nicotine (3) the second-generation penlike device (1.0 O, eGo-One by Joyetech) with strawberry flavouring and 1.2% nicotine (4) the second-generation penlike device (1.0 O, eGo-One by Joyetech) with strawberry flavouring and 0% nicotine (5) a sham The authors concluded that the acute sympathomimetic effect of e-cigarettes is attributable to the inhaled nicotine, not to non-nicotine constituents in e-cigarette aerosol, recapitulating the same heart rate variability pattern associated with increased cardiac risk in multiple populations with and without known cardiac disease. Evidence of oxidative stress, as estimated by plasma paraoxonase activity, was not uncovered following acute e-cigarette exposure.	Randomised crossover trial
Chaumont *et al.*[345] 2018	Harm	The authors reported on the **differential effects of e-cigarettes (specifically the differential effects of vehicles, propylene glycol and glycerol, and nicotine) on macro and microvascular function, arterial stiffness, and oxidative stress.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette occasional users (median cumulative pack-years: 0.2) using: (1) e-cigarette with e-liquid which was nicotine free (0 mg.ml−1) (2) e-cigarette with e-liquid 3 mg/ml−1 (3) sham vaping The authors concluded that high-temperature e-cigarette vehicle vaporisation does not alter micro- and	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		macrovascular function or oxidative stress, and that these effects are solely attributable to nicotine.	
Franzen *et al.* [350] 2018	Harm	The authors reported on the relationship **of e-cigarettes and cigarettes with peripheral and central haemodynamics, as well as arterial stiffness.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (current, without a history of vaping or dual use) with: (1) e-cigarette with nicotine the eGo-T CE4 vaporizer (third generation) 24 mg/mL nicotine tobacco flavour (2) e-cigarette with 0 mg/mL nicotine tobacco flavour (3) conventional combustible tobacco cigarette (Philip & Morris) The authors concluded that there were changes in peripheral and central blood pressure and also in pulse wave velocity after smoking a conventional combustible tobacco cigarette as well as after vaping a nicotine-containing e-cigarette. These findings may be associated with an increased long-term cardiovascular risk.	Randomised controlled trial
Mastrangeli *et al.* [344] 2018	Harm	The authors reported on the relationship of **conventional combustible tobacco cigarettes and e-cigarettes with oxidative stress and endothelial dysfunction**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked a mean of 11.1 cigarettes per day for a mean of 6.4 years at baseline) using: (1) e-cigarette with a mean nicotine content of 16mg (2) conventional tobacco cigarette with a mean nicotine content of 0.6mg The authors reported that absolute changes in oxidative stress and vascular features after smoking a conventional combustible tobacco cigarette and vaping an e-cigarette were significantly associated, with the notable exception of 8-iso-prostaglandin F2α-III levels The authors also stated that this post hoc analysis of the SUR-VAPES 1 trial suggests that the comparative oxidative and vascular effects of e-cigarettes versus conventional combustible tobacco cigarettes may be influenced by smoking status, with a potential interaction due to oral contraceptives.	Non-randomised before and after study
Nocella *et al.* [354] 2018	Harm	The authors reported on the impact of **conventional combustible tobacco cigarette versus e-cigarette smoking on platelet function.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoked a mean of 11.1 cigarettes per day for a mean of 6.4 years at baseline) using: (1) conventional combustible tobacco cigarette users with a mean nicotine content of 0.6 mg (2) e-cigarette with a nicotine cartridge with a mean nicotine content of 16 mg The authors concluded that in smokers, there were no significant changes in sCD40L and sP-selectin, but there was a significant increase in platelet aggregation. In non-smokers, there was a significant increase in all markers of platelet activation following both conventional combustible tobacco cigarette and e-cigarette use. Both conventional combustible tobacco cigarette and e-cigarettes have short-term effects on platelet activation, although in non-smokers the use of e-cigarettes had a less important impact on platelet function.	Non-randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
Pywell *et al.*[357] 2018	Harm	The authors reported on the **effect of e-cigarettes on hand microcirculation.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (average consumption 1.5 packs per week at baseline) using: (1) e-cigarette nicotine 24 mg (2) e-cigarette with no nicotine 0 mg Comparison(s) of non-smokers using: (1) e-cigarette nicotine 24 mg (2) e-cigarette with no nicotine 0 mg The authors concluded that a 24 mg e-cigarette significantly reduced smokers' hand microcirculation during and after smoking. Microcirculation increased in smokers after inhalation of a 0 mg e-cigarette. The authors advised smokers undergoing hand surgery to avoid high-dose e-cigarettes and, if necessary, to use 0 mg e-cigarettes as an alternative.	Non-randomised before and after study
Spindle *et al.*[351] 2018	Harm	The authors reported on the **effects of the e-cigarette liquid solvents propylene glycol and vegetable glycerine on user nicotine delivery**, heart rate, subjective effects, and puff topography. *Comparative groups* Comparison(s) of dual users (e-cigarette and conventional combustible tobacco cigarette) (who smoked < 5 cigarettes daily, and used their e-cigarette for ≥ 3 months and vaped ≥ 1 ml of ≥ 6 mg/ml nicotine concentration liquid daily at baseline) with: (1) eGo Cartomizers filled with 1 ml of e-cigarette liquid containing 18 mg/ml of nicotine where the difference was with the liquid propylene glycol: vegetable glycerine ratio 100:0 (2) eGo Cartomizers filled with 1 ml of e-cigarette liquid containing 18 mg/ml of nicotine where the difference was with the liquid propylene glycol: vegetable glycerine ratio 70:30 (3) eGo Cartomizers filled with 1 ml of e-cigarette liquid containing 18 mg/ml of nicotine where the difference was with the liquid propylene glycol: vegetable glycerine ratio 30:70 (4) eGo Cartomizers filled with 1 ml of e-cigarette liquid containing 18 mg/ml of nicotine where the difference was with the liquid propylene glycol: vegetable glycerine ratio 0:100 The authors concluded that the ratio of liquid propylene glycol to vegetable glycerine influenced nicotine delivery, some subjective effects, and puff topography. Lower overall product satisfaction associated with the 100% propylene glycol liquid suggests that factors other than nicotine delivery (aerosol visibility) may play a role in maintaining e-cigarette use. Regulating e-cigarette acute effects, such as nicotine delivery, and subjective effects may require simultaneous attention to the ratio of liquid propylene glycol to vegetable glycerine, as well as device, liquid, and behavioural factors known to influence these outcomes. The participants' heart rates increased significantly after use.	Non-randomised crossover trial
Antoniewicz *et al.*[356] 2019	Harm	The authors reported on the **acute effects of e-cigarette inhalation on the vasculature and the conducting airways.** Comparative groups Comparison(s) of conventional combustible tobacco cigarette occasional users (maximum 10 cigarettes per month at baseline) with: (1) e-cigarette with 19mg/ml nicotine (2) e-cigarette with 0mg/ml nicotine The authors concluded that inhaled e-cigarette aerosol with nicotine has an acute negative impact on vascular and	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		pulmonary function, and that chronic usage may lead to long-term adverse health effects.	
Cossio *et al.* [349] 2020	No benefit or harm	The authors reported on the effects of a **single bout of e-cigarette use on vascular measures of health.** *Comparative groups* Comparison(s) of e-cigarette themselves (in young healthy participants who were naive to any tobacco products) using: (1) e-cigarette with nicotine (2) e-cigarette without nicotine, and (3) placebo control (menthol flavoured cigarette-like pipe) The authors concluded that there were no significant changes in heart rate, systolic and diastolic blood pressure, endothelial function (via flow-mediated dilation), or arterial stiffness (cardio-ankle vascular index) throughout the experiment.	Randomised crossover trial
Sumartiningsih *et al.* [352] 2019	Harm	The authors examined the **exercise-induced heart rate response and heart rate variability in subjects caused by inhaling smoke from tobacco cigarettes and aerosolised vapour from e-cigarettes**. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (regular, smoking a mean of 9.2 (SD ± 1.3) cigarette per day for a mean duration of 3.5 years) using: (1) 0 mg/mL nicotine e-cigarette (2) 3 mg/mL nicotine e-cigarette (3) Two tobacco cigarettes with 1.5 mg nicotine each which equals 3 mg. The authors concluded that a significant acute autonomic cardiac modulation during exercise is induced by an acute episode of e-cigarette and tobacco cigarette smoking.	Randomised crossover trial
Chaumont *et al.*[358] 2020	Harm	The authors reported on the **acute effects of vaping and their reversibility on biological/clinical cardio-respiratory parameters** (serum/urine pneumoproteins, haemodynamic parameters, lung function test and diffusing capacities, transcutaneous gas tensions (primary outcome), and skin microcirculatory blood flow). *Comparative groups* Comparison of e-cigarette users themselves exclusive nicotine e-cigarette use for ≥ 1 year at baseline) using: (1) e-cigarette with nicotine (2) e-cigarette without nicotine (3) cessation of e-cigarette The authors concluded that short-term e-cigarette cessation by regular users decreases baseline heart rate and lung inflammation and increases forced expiratory flow by 25%, suggesting that high-wattage vaping alters airway function. Urine metabolomic signature was also slightly modified by this short-term e-cigarette cessation. Acute nicotine and nicotine-free vaping decreased transcutaneous oxygen tensions likely as a result of gas exchange disturbances. Finally, only acute nicotine vaping increased systolic blood pressure, diastolic blood pressure, and heart rate.	Randomised crossover trial

4.4.2.3 Cancers: interventional trials

There were no interventional trials on the relationship between e-cigarettes and cancer outcomes.

4.4.2.4 Respiratory diseases: interventional trials

There were 16 interventional trials reporting on the relationship between e-cigarette use and respiratory disease outcomes (Table 49). Broadly, the outcomes can be grouped as measures of tissue damage or stress; measures of respiratory function, including functional impairment; symptoms of ill health; and measures of toxicity in body tissue and exhaled breath. The outcomes assessed included:

- Indices of endothelial activation in human pulmonary microvascular endothelial cells, oxidative stress, alveolar macrophages tissue, hypoxia and lower airway injury symptoms, inflammation parameters, and levels of C-reactive protein
- Pulmonary function tests, such as forced expiratory volume in 1 second and forced vital capacity, and their ratio; forced expiratory flow and forced oscillation technique, resonant frequency, reactance area, inspiratory capacity, tidal volume, and respiratory rate
- Plasma endothelial microparticles
- Signs and symptoms: cough; phlegm; urge-to-cough sensation, specifically the urge-to-cough threshold; cough reflex sensitivity; chest tightness; breathlessness; secretions; wheezing; sinonasal symptoms and nasal mucociliary clearance; and shortness of breathExhaled nitric oxide, fractional concentration of carbon monoxide in exhaled breath, and oxygen saturation.

Taken together, the 16 trials reported discordant findings. One paper concluded that smokers invited to switch to e-cigarettes who completely abstained from smoking showed steady progressive improvements in their exhaled breath measurements and symptom scores.[359] Two papers concluded that e-cigarettes did not negatively affect lung function.[360 361] Five papers reported that e-cigarettes were less harmful to lung function than conventional tobacco cigarettes,[362-365 366] and one of these studies suggested that e-cigarette use may reverse negative respiratory outcomes in former smokers.[364] However, nine papers suggest that e-cigarettes damage the respiratory system by reducing vascular function to the lungs and/or reducing physiological function.[365 367-374]

Two of the trials reported on the relationship between e-cigarettes and measures of tissue damage which were assessed as oxidative stress, and indicated a discordance in the nature and direction of the relationship. The first study reported that even in the absence of nicotine, acute e-cigarette aerosol inhalation can lead to a transient increase in oxidative stress and inflammation.[373] According to the trial authors, this can adversely affect the vascular endothelial network by promoting oxidative stress and immune cell adhesion; they concluded that e-cigarette inhalation has the potential to drive the onset of vascular pathologies. In the second study, the authors concluded that although endothelial microvascular function and oxidative stress remained unaffected, acute vaping of an aerosol of propylene glycol/glycerol at high wattage and in large quantities induced a sustained tissue hypoxia, airway epithelial injury, and small airway constriction.[370]

Table 49 Interventional trial papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
Vardavas *et al.*[367] 2012	Harm	The authors reported on the **short-term pulmonary effects of using an e-cigarette, including: impact on respiratory flow resistance, impedance, and exhaled nitric oxide.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (with a minimum pack-year index of 5 at baseline) using: (1) e-cigarette with a cartridge NOBACCO MLB-MED with a dose of 11 mg nicotine (2) control group e-cigarette without a cartridge The authors concluded that the e-cigarettes assessed in the context of this study had immediate adverse physiological effects after short-term use comparable to some of the effects seen with tobacco smoking.	Non-randomised trial

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
Flouris *et al.*[362] 2013	Less harmful than conventional combustible tobacco cigarettes	The authors conducted a comprehensive and standardised assessment of the **acute impact of active and passive e-cigarette smoking on serum cotinine and lung function** (plus toxins). *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoking ≥15 cigarettes per day at baseline) using: (1) a control session (ACTIVECON) (2) an active tobacco cigarette smoking session (ACTIVETOB) smoking participant favourite brand (3) an active e-cigarette smoking session (ACTIVEE-CIG) using the model: Giant, Nobacco with a ''tobacco taste'' and containing 11 mg/ml of nicotine Comparison(s) of never smokers using the same 3 interventions The authors concluded that, regarding short-term usage, the studied e-cigarettes generate smaller changes in lung function than, but a similar nicotinergic impact as, tobacco cigarettes. Future research should target the health effects of long-term e-cigarette usage, including the effects of nicotine dosage.	Non-randomised controlled trial
Ferrari *et al.*[363] 2015	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **short-term effects of a nicotine-free e-cigarette compared to a conventional combustible tobacco cigarette in smokers and non-smokers.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (with a minimum pack-year index of 5 at baseline) using: (1) nicotine free e-cigarette (ELIPS C Series) (2) traditional cigarettes (a commercial 'popular brand' Marlboro Red Label Box Comparison(s) of non-smokers (not defined) using the same two interventions The authors concluded that the specific brand of nicotine-free e-cigarettes used in this study was not associated with major acute physiological changes, causing only small (albeit statistically significant) decreases in forced expiratory flow (FEF) 25% and forced expiratory volume in the first second (FEV1) in the group of smokers. By contrast, smoking a conventional combustible tobacco cigarette induced immediate bronchoconstriction in non-smokers.	Randomised crossover trial
Campagna *et al.*[359] 2016	Benefit	The authors reported on changes in breathomics (breath-based diagnostics) from **a 1-year randomised smoking cessation trial of e-cigarettes** fractional nitric oxide concentration in exhaled breath (FeNO), exhaled carbon monoxide, and symptom scores). *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (median cigarette per day 20.0 and median pack-years 24.9; smoke ≥ 10 tobacco cigarettes per day for ≥ 5 years and not intending to quit at baseline) with: (1) first-generation cigarette-lookalike e-cigarette ('Categoria'; Arbi Group Srl, Seregno, Italy 'Original 2.4%' (2.27% nicotine) (2) 'Categoria 1.8%' (1.71% nicotine) (3) 'Categoria Original 0%' nicotine ('sweet tobacco' aroma) The authors concluded that smokers who were invited to switch to e-cigarettes who completely abstained from smoking showed steady progressive improvements in their exhaled breath measurements and symptom scores. Fractional exhaled nitric oxide and exhaled carbon monoxide normalisation is highly supportive of improved	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
		respiratory health outcomes and adds to the notion that quitting tobacco smoking can reverse harm in the lungs.	
Cibella *et al.*[360] 2016	Benefit	The authors reported on **lung function and respiratory symptoms in a randomised smoking cessation trial** of e-cigarettes, presented on the basis of participants' pooled continuous smoking phenotype classification (quitters, reducers, or failures). *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (median cigarette per day 20.0 and median pack-years 24.9; smoke ≥ 10 tobacco cigarettes per day, for ≥ 5 years and not intending to quit at baseline) using: (1) first-generation cigarette-lookalike EC ('Categoria'; Arbi Group Srl, Seregno, Italy 'Original 2.4%' (2.27% nicotine) (2) 'Categoria 1.8%' (1.71% nicotine) (3) 'Original 0%' without nicotine ('sweet tobacco' aroma). The authors concluded that this 1-year prospective RCT shows improvements in spirometric indices of peripheral airways, as well as in respiratory symptoms in smokers who were invited to quit or reduce their cigarette consumption by switching to first-generation e-cigarettes. Specifically, the present study shows progressive and consistent improvement in forced expiratory flow (FEF) 25–75% among those who completely gave up cigarette smoking. Improvements in FEF 25–75% from baseline were no different in quitters who stopped using e-cigarettes compared with quitters who were still using e-cigarettes.	Randomised controlled trial
Dicpinigaitis *et al.*[368] 2016	Harm	The authors reported on the **effect of e-cigarette use on the urge-to-cough** sensation, specifically the urge-to-cough threshold, and cough reflex sensitivity. *Comparative groups* Comparison(s) of never conventional combustible tobacco cigarette users using: (1) disposable e-cigarette (Blu, Classic Tobacco flavour, Lorillard Technologies, Greensboro) (2) disposable Blu e-cigarette contains 20–24 mg of nicotine The authors concluded that a single exposure to an e-cigarette significantly inhibits the urge-to-cough threshold as measured by capsaicin cough challenge testing. These findings add to the growing body of evidence that e-cigarette vapour is not a physiologically benign substance and support further investigation of the effects of repeated or chronic use of e-cigarettes on cough sensitivity and other respiratory parameters.	Non-randomised before and after study
Kumral *et al.*[369] 2016	Harm	The authors reported on the impact of **e-cigarette smoking on sinonasal symptoms and nasal mucociliary clearance.** *Comparative groups* Comparison of e-cigarette users themselves with: (1) e-cigarette with a medium density (11-12 mg/ml) liquid Comparison(s) of exclusive conventional combustible tobacco cigarette users (smoked 1 pack of cigarettes per day for ≥5 years (mean 9.7 years) and willing to quit smoking at baseline) and dual users (e-cigarettes and conventional combustible tobacco cigarette who smoked 1 pack of cigarettes per day for ≥5 years (mean 9.8 years)using: (1) e-cigarette with a medium density (11-12 mg/ml) liquid The authors concluded that although e-cigarettes are widely used as a method of quitting smoking, they have negative effects on sinonasal symptoms and mucociliary clearance.	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
Boulay *et al.*[361] 2017	No harm or benefit	The authors reported on the acute **effects of nicotine-free and flavour-free e-cigarette use on lung functions** in healthy and asthmatic individuals. *Comparative groups* Comparison(s) of never smokers (who were not active e-cigarette users at baseline) using: (1) e-cigarette with nicotine-free and flavour-free liquid (2) e-cigarette without liquid The authors concluded that a 1-hour inhalation session of a high-grade and contaminant-free mixture of propylene glycol and glycerol using a commercially available e-cigarette, performed in a controlled environment, does not significantly impact pulmonary function or symptoms in either healthy or asthmatic subjects.	Non-randomised crossover trial
D'Ruiz *et al.*[364] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship between **partial or complete substitution of cigarettes with e-cigarettes** in adult smokers with measurements of cardiovascular and pulmonary function endpoints and other physiological effects. *Comparative groups* Comparison of dual users (conventional combustible tobacco cigarettes and e-cigarettes) using: 1) close system rechargeable blu e-cigarette tobacco flavour 24 mg/mL nicotine (2) close system rechargeable blu e-cigarette cherry flavour 24 mg/mL nicotine (3) close system disposable blu e-cigarette cherry flavour 24 mg/mL nicotine Comparison of e-cigarette users themselves (exclusive at baseline) with: (1) close system rechargeable blu e-cigarette tobacco flavour 24 mg/mL nicotine plus usual brand combustible tobacco cigarettes (2) close system rechargeable blu e-cigarette cherry flavour 24 mg/mL nicotine plus usual brand combustible tobacco cigarettes (3) close system disposable blu e-cigarette cherry flavour 24 mg/mL nicotine plus usual brand combustible tobacco cigarettes The authors concluded that use of e-cigarettes for 5 days under the various study conditions did not lead to higher blood pressure or heart rate values, negative respiratory health outcomes, or serious adverse health events. Reductions in blood pressure and heart rate vital signs were observed in most of the participants who either ceased tobacco and nicotine product use altogether or switched completely to using e-cigarettes. Pulmonary function tests showed small but non-statistically significant improvements in forced vital capacity and forced expiratory volume in most usage groups. Statistically significant (p<0.05) benefits associated with smoking reduction were also noted in exhaled carbon monoxide and fractional nitric oxide concentration in exhaled breath. All studied products were well tolerated. The study findings suggest that there are potential cardiovascular and pulmonary function benefits when smokers switch to using e-cigarette products.	Randomised controlled trial
Chaumont *et al.* [370] 2018	Harm	The authors reported on the relationship of **high-wattage e-cigarettes with tissue hypoxia and lower airway injury.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette occasional users (median cumulative pack years 0.25 at baseline) with: (1) e-cigarette with a propylene glycol and glycerol mix (50:50) mix	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
		The authors concluded that although endothelial microvascular function and oxidative stress remained unaffected, acute vaping of an aerosol of propylene glycol/glycerol at high wattage and in a large amount induced sustained tissue hypoxia, airway epithelial injury, and small airway constriction.	
Coppeta *et al.* [365] 2018	E-cigarette use only less harmful than conventional combustible tobacco cigarettes Dual use may be more harmful than conventional combustible tobacco cigarettes	The authors examined whether the **active use of e-cigarettes** in healthy subjects can cause **short-term effects on lung function**, and whether these effects are different from those associated with a similar exposure to tobacco smoke. *Comparative groups* Comparison(s) of non-smokers (who were healthy volunteers) with: (1) e-cigarette containing e-liquid 18mg/ml nicotine model EGO P(L) (2) tobacco cigarette (not specified in summary) The authors concluded that the active use of e-cigarettes for a short time caused similar, although less pronounced, effects as tobacco smoke on pulmonary function. Similarly, the particles released in the environment had a lower concentration and persistence than those of tobacco cigarettes. These data suggest that e-cigarettes may potentially be dangerous for active smokers and the environment.	Non-randomised before and after study
Lappas *et al.*[371] 2018	Harm	The authors investigated the duration of **immediate respiratory effects of e-cigarette smoking** and tested the hypothesis that e-cigarette smoking has more prominent effects in asthmatics compared with healthy smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 1 cigarette during the past 30 days) with e-cigarette users themselves using (≥ 1 ml of liquid per day with a nicotine concentration of ≥ 12 mg/mL and used their device for ≥ three months) with: (1) the new generation e-cigarette with nicotine 1.18% and tobacco essence The authors concluded that a single session of e-cigarette smoking had immediate mechanical and inflammatory respiratory effects in healthy smokers and in asymptomatic smokers with intermittent asthma. These actions persisted for 15 to 30 minutes (fractional nitric oxide concentration in exhaled breath). The intensity and duration of these changes were more prominent in individuals with intermittent asthma.	Non-randomised crossover trial
Staudt *et al.*[372] 2018	Harm	The authors reported on the **altered lung biology of healthy never-smokers following acute inhalation of e-cigarettes.** *Comparative groups* Comparison(s) of never smokers using: (1) the e-cigarette “Blu” with nicotine (2) the e-cigarette “Blu” without nicotine The authors concluded that even limited, acute exposure to e-cigarette aerosols dysregulates the biology of the human lung in vivo. Whether or not chronic exposure to e-cigarettes will result in lung disease is unknown and can only be evaluated by large-scale, long-term trials of individuals who are not former or current cigarette smokers who have used only e-cigarettes, a study that would be challenging to carry out at present, as most e-cigarette users have had prior or current cigarette smoke exposure.	Controlled trial with unequal randomisation

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Trial design
		However, the observed changes in the biology of the small airway epithelium, alveolar macrophages, and (indirectly) lung capillary endothelium may signal that e-cigarette use may not be as safe as has been assumed.	
Barna *et al.*[366] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors aimed to examine the **effects of combustible and non-combustible methods of smoking on lung function** based on functional respiratory tests and the degree of alveolocapillary membrane damage, measured by dynamic inhalation scintigraphy. *Comparative groups* Comparison of e-cigarette user (who currently using e-cigarettes with 10 mg nicotine/ml and were previously heavy conventional combustible tobacco cigarette smokers) with: (1) conventional combustible tobacco cigarettes with participants smoking 20 to 25 cigarettes per day for one week The authors concluded that e-cigarette smoking is less harmful to lung function than conventional combustible tobacco cigarette smoking, and that it can be recommended to heavy smokers who are unable to stop smoking.	Non-randomised before and after study
Chatterjee *et al.*[373] 2019	Harm	The authors reported on the **acute response to aerosol inhalation of non-nicotinised e-cigarettes** in terms of oxidative stress and indices of endothelial activation in **human pulmonary microvascular endothelial cells**. *Comparative groups* Comparison(s) of non- smokers (conventional combustible tobacco cigarette) with: (1) e-cigarette E-puffer an eco-disposable nicotine device The authors concluded that the findings suggest that even in the absence of nicotine, acute e-cigarette aerosol inhalation leads to a transient increase in oxidative stress and inflammation. This can adversely affect the vascular endothelial network by promoting oxidative stress and immune cell adhesion. Thus, e-cigarette inhalation has the potential to drive the onset of vascular pathologies.	Non-randomised before and after study
Kerr *et al.*[374] 2019	Harm	The authors reported on the acute **effects of electronic and tobacco cigarettes on vascular and respiratory function** in healthy volunteers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (Mean: 7 per day and ≥ 1 tobacco cigarettes per day) using: (1) the habitual conventional combustible tobacco cigarette of study participants (which comprised one of six brands) (2) second-generation e-cigarette device with 18 mg/ml nicotine and tobacco flavoured The authors concluded that acute exposure to tobacco smoking as well as to e-cigarettes influences vascular and respiratory function. Where tobacco smoking significantly increased microparticle formation, indicative of possible endothelial injury, e-cigarette use induced vasoreactivity and decreased peak expiratory flow. These findings suggest that both e-cigarette and tobacco smoking negatively impact vascular and respiratory function.	Randomised crossover trial

4.4.2.5 Oral diseases: interventional trials

Three interventional trial papers reported on the association between e-cigarette use and oral health outcomes (Table 50). Outcomes were perfusion of buccal mucosal tissue,[375] gingival inflammation,[376] and a valid method to measure parent drug and metabolites in oral fluid.[377]

One trial reported that e-cigarettes may improve blood flow to the oral mucosa, although further trials are needed to show whether they improve healing time after surgery.[375] The authors of another trial concluded that there was a statistically significant increase in gingival inflammation when tobacco smokers switched from smoking to vaping for 2 weeks.[376]

Table 50 Interventional trial papers on oral diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on oral diseases	Trial design
Reuther *et al.*[375] 2016	Benefit	The authors reported on the immediate **effects of e-cigarettes on perfusion in buccal mucosal tissue in non-smokers.** *Comparative groups* Comparison of volunteers (who were currently non-smokers, of note, other smoking and e-cigarette related behaviours were not described in summary) using: (1) e-cigarette containing no nicotine in e-liquid (2) e-cigarette continuing 16 mg nicotine in e-liquid The authors concluded that e-cigarettes may influence blood flow to the oral mucosa, although further trials are needed to show whether they improve healing time after surgery.	Non-randomised before and after study
Wadia *et al.*[376] 2016	Harm	The authors reported findings from a pilot study on **gingival response when smokers switched from smoking to vaping.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 10 tobacco cigarettes per day, for ≥ 5 years and not intending to quit at baseline) with: (1) blu PRO e-cigarette with 18mg nicotine The authors concluded that there was a statistically significant increase in gingival inflammation when tobacco smokers switched from smoking to vaping for 2 weeks, but results should be interpreted with extreme caution since this was only a pilot study.	Non-randomised before and after study
Papaseit *et al.*[377] 2017	No harm or benefit	The authors reported on findings following the **monitoring of nicotine intake from e-cigarettes**; specifically, the **measurement of parent drug and metabolites in oral fluid and plasma.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 3 tobacco cigarettes per day, for ≥ 1 year and not tried e-cigarettes at baseline) using: (1) a second-generation e-cigarette (Nhoss®, e-liquid 16 mg/mL nicotine, flavour "blond", France) (2) tobacco cigarette (Marlboro®, 0.8 mg nicotine per cigarette, USA) The authors concluded that the obtained results support the measurement of nicotine and metabolites in oral fluid in the assessment of intake after e-cigarette use and appear to be a suitable alternative to plasma when monitoring nicotine delivery from e-cigarettes for clinical and toxicological trials.	Randomised, crossover trial

4.4.2.6 Developmental and reproductive effects: interventional trials

There were no interventional trials on the association between e-cigarette use and developmental and reproductive effects outcomes.

4.4.2.7 Injuries and poisonings: interventional trials

There were no interventional trials on the relationship between e-cigarettes and injuries or poisonings outcomes.

4.4.2.8 Exposure to e-cigarette toxins: interventional trials

There were 13 interventional trials reporting on the relationship between e-cigarettes and exposure to e-cigarette toxins outcomes (Table 51). The trials measured the toxicants – including nicotine equivalents, major nicotine metabolites, and a range of other volatile organic compounds – and assessed biomarkers of harmful and potentially harmful constituents of e-cigarette toxicants. A list of harmful and potentially harmful constituents is presented in Appendix 8.

The outcomes assessed included:

- Nicotine exposure, measured by the following nicotine metabolites: 3-hydroxycotinine, cotinine, nicotine, cotinine N-oxide, nicotine N-oxide, norcotinine, nornicotine, and nicotine equivalents
- Tobacco exposure, measured by the following nitrosamine: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)
- Selected carcinogens and toxicants, measured as biomarkers of urine concentration
- Toxic gases, including exhaled carbon monoxide and carboxyhaemoglobin

Eight trials reported that toxin levels associated with smoking conventional tobacco cigarettes were lower in persons who had switched from using conventional tobacco cigarettes to using e-cigarettes.[378-385] Three studies examined e-cigarettes' ability to deliver nicotine and concluded that it was not as good as the conventional cigarette,[384 386 387] but two of these studies reported they was as good as or better than nicotine replacement therapy products.[384 387] One paper reported that e-cigarette users had higher concentrations of methylating agent metabolites[388] and another paper reported that e-cigarettes negatively impacted psychomotor performance, and, in some instances, produced detectable levels of a urine alcohol metabolite.[389]

Table 51 Interventional trial papers on exposure to e-cigarette toxins, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
van Staden *et al.*[378] 2013	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **carboxyhaemoglobin levels, and on health and lifestyle perceptions in smokers converting from tobacco cigarettes to e-cigarettes.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (median cigarette per day 20.0 [range 10-30]and median spending on cigarettes R700 [range R400 - R1000] per month; heavy and longstanding smokers at baseline) with: (1) Twisp e-cigarette The authors concluded that smoking the Twisp e-cigarette may be a healthier and more acceptable alternative to smoking tobacco cigarettes.	Non-randomised before and after study
Hajek *et al.*[387] 2015	Not adequate for benefit	The authors reported on the **nicotine intake from e-cigarettes** following initial use and after 4 weeks of regular use. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean cigarettes per day 25, interested in quitting and not having previously used e-cigarettes for ≥1 week at baseline) with: (1) a first-generation Green Smoke e-cigarette with cartridges labelled 2.4% nicotine tobacco flavoured The authors concluded that first-generation e-cigarettes provide faster nicotine absorption than nicotine replacement products, but to compete successfully with conventional combustible tobacco cigarettes, e-cigarettes may need to provide higher doses of nicotine. Nicotine intake from e-cigarettes can increase with practice, but further trials are needed to confirm this effect.	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
McRobbie *et al.*[379] 2015	Less harmful than conventional combustible tobacco cigarettes	The authors investigated **exposure to carbon monoxide (CO), nicotine (by measuring cotinine in urine), and acrolein (by measuring its primary metabolite, S-(3-hydroxypropyl) mercapturic acid (3-HPMA) in urine) in smokers and e-cigarette users.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (interested in quitting and not having previously used e-cigarettes for ≥1 week at baseline) using: (1) a first-generation Green Smoke e-cigarette with cartridges labelled 2.4% nicotine tobacco flavoured which was used exclusive for four weeks (2) a first-generation Green Smoke e-cigarette with cartridges labelled 2.4% nicotine tobacco flavoured which was used in combination with conventional tobacco cigarettes for four weeks The authors concluded that a significant reduction in carbon monoxide was observed in e-cigarette users and dual users of e-cigarettes and conventional combustible tobacco cigarettes. Cotinine levels also declined, but to a lesser extent at 17% decrease compared to their baseline measure; and dual users at 44% decrease. Mean acrolein (3-HPMA) levels had decreased at 4 weeks, with a 79% decrease in e-cigarette-only users compared to their baseline measure and a 60% decrease in dual users. In dual users, e-cigarette use significantly reduced exposure to carbon monoxide and acrolein because of a reduction in smoke intake. E-cigarettes may reduce harm even in smokers who continue to smoke, but long-term follow-up trials are needed to confirm this.	Non-randomised before and after study
O'Connell *et al.*[380] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **reductions in biomarkers of exposure to harmful or potentially harmful constituents** following partial or complete substitution of cigarettes with e-cigarettes in adult smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 10 tobacco cigarettes per day for ≥ 1 year and never previously used e-cigarettes at baseline) using: (1) a closed system rechargeable blu e-cigarette with tobacco flavour (2) a closed system rechargeable blu e-cigarette with cherry flavour (3) a closed system disposable blu e-cigarette with to cherry tobacco flavour The authors concluded that the levels of urinary biomarkers in subjects who completely substituted their usual conventional combustible tobacco cigarettes with e-cigarettes were significantly lower (29–95%) after 5 days. Percentage reductions in eight of nine urinary biomarkers of exposure were indistinguishable from smokers who had quit smoking, except for nicotine equivalents, which declined by 25–40%. Dual users who halved self-reported daily cigarette consumption by replacing them with e-cigarettes exhibited reductions (7–38%) in eight of nine urinary biomarkers but had increased (1–20%) nicotine equivalents. Reductions were broadly proportional to the reduced numbers of cigarettes smoked. Dual user urinary nicotine equivalents were slightly higher when compared to other groups (e-cigarette only group and non-user or cessation group), but not statistically significant. After 5 days, blood nicotine biomarker levels were lower in the and non-user or cessation group (75–96%) and exclusive e-cigarette use group (11–83%), with dual users experiencing no significant reductions. All subjects experienced significant decreases in exhaled carbon	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
		monoxide; these decreases in the cessation and exclusive use groups ranged from 88–89%, and from 27–32% in dual users. Exhaled fractional nitric oxide concentration in exhaled breath (FeNO) increased in the cessation and exclusive use groups (46% and 63%, respectively), whereas the dual users experienced minimal changes. Overall, smokers who completely or partially substituted conventional combustible tobacco cigarettes with e-cigarettes over 5 days experienced reductions in harmful or potentially harmful constituents.	
Poulianiti *et al.*[390] 2016	Equal harm	The authors reported on **acute active and e-cigarette changes on antioxidant responses and subsequent pathologies measuring redox status.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 15 tobacco cigarettes per day at baseline) using: (1) a control session (2) an active tobacco cigarette smoking session (smoked 2 cigarettes within 30-min) Comparison(s) of non -smokers (conventional combustible tobacco cigarette) using: (1) a control session (2) a passive tobacco cigarette smoking session (exposure of 1 h to 23 ± 1ppm of CO in a 60m3 environmental chamber) (3) a passive e-cigarette smoking session (exposure of 1 h to air enriched with pre- determined number of puffs in a 60m3 environmental chamber The authors concluded that tobacco and e-cigarette smoking exposure do not acutely alter the response of the antioxidant system, under either active or passive smoking conditions. Overall, there is no distinction between tobacco and e-cigarette active and passive smoking effects on specific redox status indices.	Randomised crossover trial
Valentine *et al.*[389] 2016a	Harm	The authors reported on the **effects of alcohol-containing e-cigarettes** on young adult smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (daily or sometimes use of cigarettes in the past six months [mean smoking years: 8.7 years] and use of an e-cigarette ≥ 1 in the previous year) using: (1) the Joyetech eGo-C without measurable levels of alcohol (2) the Joyetech eGo-C with 0.1 to 0.7% alcohol (3) the Joyetech eGo-C with 1.0 to 3.0% alcohol (4) the Joyetech eGo-C with 23.5% alcohol The authors concluded that brief use of a widely available type of e-cigarette containing an e-liquid purchased from an Internet vendor can negatively impact psychomotor performance and, in some instances, produce detectable levels of a urine alcohol metabolite.	Randomised, crossover trial
Goniewicz *et al.*[381] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the relationship of **e-cigarettes with a range of carcinogens and toxicants.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥ 5 tobacco cigarettes per day for ≥ 1 year and able to use e-cigarettes safely at baseline) with: (1) a pen-style M201 e-cigarettes with 11.0mg of nicotine and tobacco-flavoured The authors concluded that the study showed that after switching from tobacco to e-cigarettes, nicotine exposure remains unchanged, while exposure to selected carcinogens and toxicants is substantially reduced. These findings suggest that e-cigarettes may effectively reduce exposure to toxic and	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
		carcinogenic substances among smokers who switched to e-cigarette products.	
Wagener *et al.*[382] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **nicotine delivery profiles and harmful constituent exposures** of second-generation and third-generation **e-cigarette users.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean cigarette per day 18.4; exclusive smoker for ≥ 3 months) using: (1) e-cigarette users used their own device and e-liquid with their preferred flavour and nicotine concentration. (2) third- (G3) e-cigarette device (3) second-generation (G2) e-cigarette devices Comparison of e-cigarette users themselves (who were exclusive, using same style of e-cigarette non-modified G2 device for ≥ 3 months) or (who were exclusive, using same style of e-cigarette non-modified G3 device for ≥ 3 months) using: (1) e-cigarette users used their own device and e-liquid with their preferred flavour and nicotine concentration. (2) third- (G3) e-cigarette device (3) second-generation (G2) e-cigarette devices The authors concluded that while baseline cotinine concentration levels among exclusive smokers, second-generation e-cigarette users, and third-generation e-cigarette users are similar (which may have implications for addiction and e-cigarettes' viability as a substitute for smoking), second-generation and third-generation e-cigarette users had significantly lower levels of exposure to a potent lung carcinogen and a cardiovascular toxicant.	Non-randomised before and after study
Yuki *et al.*[386] 2017	Harm	The authors reported on the **pharmacokinetics of nicotine following the use of a prototype novel tobacco vapour product** in comparison to a conventional combustible tobacco cigarette. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean cigarette per day 18.1 and mean smoking history of 18.9 years; smoke ≥ 11 tobacco cigarettes per day for ≥ 1 year at baseline) using: (1) a prototype novel tobacco vapor (PNTV) product described as a power supply unit, a cartridge with a heater and liquid, a capsule filled with tobacco blend which generate a nicotine free vapour (2) commercially available conventional cigarette (1 mg tar and 0.1 mg nicotine) The authors concluded that the results suggest that the prototype novel tobacco vapour product shows a similar pharmacokinetic profile to conventional combustible tobacco cigarettes, while delivering less nicotine following controlled use.	Randomised crossover trial
Czoli *et al.*[383] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **relationship between tobacco and e-cigarette use with a range of biomarkers** including carbon monoxide (CO), 1-hydroxypyrene (1-HOP), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). *Comparative groups* Comparison of dual users (conventional combustible tobacco cigarette [≥5] daily and e-cigarettes daily [previous 7 days]) using: (1) dual users' session (2) tobacco cigarette users' session (3) e-cigarette users' session (4) no product user session Comparison of e-cigarettes users themselves (daily for previous 7 days) using the same four interventions. The authors concluded that although dual use may reduce exposure to tobacco smoke constituents to some extent,	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
		abstaining from smoking is the most effective way to reduce such exposure. They also stated that public health authorities should clearly communicate the relative risk of e-cigarettes and tobacco cigarettes to the general public.	
Round *et al.*[384] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the outcome levels of a range of **biomarkers of tobacco exposure after smokers switch to an e-cigarette or nicotine gum.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (who smoke ≥ 10 tobacco filtered cigarettes per day and smoke first cigarette within 30 minutes of waking at baseline) with: (1) Vuse Solo Digital Vapor Cigarettes (Original - tobacco flavour) (2) Vuse Solo Digital Vapor Cigarettes (Menthol) (3) Nicorette 4 mg nicotine gum The authors concluded that exposure to toxicants when using Vuse Solo is significantly reduced compared with combustible cigarette smoking, and these reductions are similar to those observed with use of nicotine gum. Although nicotine exposure is significantly reduced, Vuse Solo maintained closer to conventional combustible tobacco cigarette smoking compared with nicotine gum use. This research suggests that use of Vuse Solo exposes consumers to fewer and lower levels of smoke toxicants than combustible cigarettes, while still providing nicotine to the consumer.	Randomised controlled trial
Beatrice *et al.*[385] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors reported on exhaled carbon monoxide **levels in smokers after fully switching to e-cigarettes or to a tobacco heating system.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean cigarette per day 21.7 and mean smoking history of 31 years either unwilling or unable to stop smoking at baseline and requesting a switch to reduced risk products) using: (1) a low potential e-cigarette (disposable, pre-filled cartridge, low–medium supply power, nicotine 18mg/ml) (2) tobacco heating system 2.2 (sticks with mean nicotine content of 0.50 mg per stick The authors concluded that reduced levels of percentage carboxyhaemoglobin did not significantly differ between the two groups, while the tobacco heating system group had a significantly greater reduction in levels of carbon monoxide versus the e-cigarette group. Both e-cigarettes and tobacco heating systems are capable of significantly reducing exhaled carbon monoxide at least in the medium term, hence constituting a viable tobacco harm-reduction approach in smokers who are unwilling or unable to stop smoking.	Non-randomised before and after study
St. Helen *et al.*[388] 2020	Harm	The authors reported on the relationship between **e-cigarette use, conventional combustible tobacco cigarette use, and abstention from smoking with a range of volatile organic compounds** (specifically 10 mercapturic acid metabolites of volatile organic compounds). *Comparative groups* Comparisons of dual users (e cigarettes [mean times per day 8.1 and mean days used in previous month was 22.6 days] and conventional combustible tobacco cigarettes [mean per day 12.9] using: (1) ad libitum vaping using cig-a-like e-cigarette (2) ad libitum vaping using fixed-power tanks (3) ad libitum vaping using variable-power tanks (4) pod e-cigarettes all JUULs (5) e-cigarette and conventional tobacco cigarette use only	Non-randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to e-cigarette toxins	Trial design
		The authors concluded that concentrations of volatile organic compound metabolites were higher during smoking compared with during vaping, except for the methylating agents' metabolite. Metabolites of acrylamide were higher during vaping compared with abstention. The 1,3-butadiene and propylene oxide metabolites were higher in variable-power tank users compared with users of cigalikes. E-cigarettes expose users to lower levels of toxic volatile organic compounds compared with cigarette smoking. However, some e-cigarettes expose users to volatile organic compounds such as acrylamide, benzene, and propylene oxide, and may pose health risks to non-smoking users.	

4.4.2.9 Other outcomes: interventional trials

Seven interventional trials reported on in other outcomes (Table 52). The outcomes measured were puffing topography, adverse events associated with two e-cigarette brands, weight status, other disease-related outcomes, and second-hand vaping.

One paper concluded that puff topography adapted to maximise nicotine intake from e-cigarettes. [391]

Two papers reported the safety profiles of two e-cigarettes. One paper reported that in the short term, e-cigarette users had lower toxin levels (benzene, acrolein, and NNK) than those found in tobacco cigarette smokers.[392] The second paper concluded that there were few serious adverse events during the 24 months of Puritane™ use, and none were related to use of the vaping product.[393]

A single paper concluded that smokers who quit smoking by switching to e-cigarettes may limit their post-smoking cessation weight gain, with reversal in any weight gain at later timepoints. [394]

A trial with one person reported that nicotine administered via e-cigarettes may reduce levodopa-induced dyskinesia in patients with Parkinson's disease.[395]

There were two papers on second-hand smoking. Two papers reported that non-users absorbed nicotine from e-cigarettes, [396] [397] and one of these papers reported negative cardiac autonomic effects by measuring heart rate variability. [396]

Table 52 Interventional trial papers on other outcomes, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on other outcomes	Trial design
Norton *et al.*[391] 2014	Harm	The authors reported on how **initial puffing behaviours and subjective responses differ between an electronic nicotine delivery system (ENDS) and conventional combustible tobacco cigarettes.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (exclusive in the previous 30 days, smoke ≥ 10 tobacco filtered cigarettes per day and did not intend to quit at baseline) using: (1) smoking own cigarette using the portable CReSS* device (2) e-cigarette TRIO-3 first generation with 11mg nicotine using the portable CReSS* device. *The CReSS device was used to record smoking topography The authors concluded that ENDS were smoked more intensively than own brand cigarettes, but delivered significantly less nicotine and were less satisfying. These findings have implications for the viability of certain ENDS as alternatives to cigarettes.	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on other outcomes	Trial design
Cravo *et al.*[392] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors undertook a randomised, parallel group study in order to **evaluate the safety profile of an e-vapour product over 12 weeks.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke between 5 and 30 tobacco cigarettes daily at baseline) using: (1) e-vapour protype 2.0% nicotine (2) conventional cigarette From this trial, the authors reported the safety profile of an e-vapour product (2.0% nicotine) in smokers of conventional combustible tobacco cigarettes switching to using an e-vapour product for 12 weeks. During the study, no clinically significant product-related findings were observed in terms of vital signs, electrocardiogram, lung function tests, and standard clinical laboratory parameters. Adverse events reported by e-vapour product subjects were more frequent during the first week after switching to the e-vapour product. Only 6% of 1515 adverse events were judged as being probably or definitely related to an e-vapour product. Additional observations in e-vapour product subjects included a decrease in the level of urine nicotine equivalents by up to 33.8%, and decreases in the level of three biomarkers of exposure to toxicants known to be present in tobacco cigarette smokers (benzene, acrolein, and NNK). The decrease in nicotine equivalents coincided with an increase in nicotine withdrawal symptoms, measured by a questionnaire, which subsided after 2 weeks. The data presented here show the potential that e-vapour products may offer smokers looking for an alternative to tobacco cigarettes.	Randomised controlled trial
Rosbrook *et al.*[394] 2016	Harm or benefit depends on point of view	The authors reported on the **sensory effects of menthol and nicotine in an e-cigarette.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke menthol flavoured tobacco cigarettes daily for ≥ 1 year at baseline) with e-cigarettes containing: (1) 0 mg/ml nicotine and 0% menthol (2 0 mg/ml nicotine and 0.5% menthol (3) 0 mg/ml nicotine and 3.5% menthol (4) 6 mg/ml nicotine and 0% menthol (5) 6 mg/ml nicotine and 0.5% menthol (6) 6 mg/ml nicotine and 3.5% menthol (7 12 mg/ml nicotine and 0% menthol (8) 12 mg/ml nicotine and 0.5% menthol (9) 12 mg/ml nicotine and 3.5% menthol (10) 18 mg/ml nicotine and 0% menthol (11) 18 mg/ml nicotine 0.5% menthol (12) 18 mg/ml nicotine 3.5% menthol (13) 24 mg/ml nicotine and 0% menthol (14) 24 mg/ml nicotine and 0.5% menthol The authors concluded that menthol can potentially improve the appeal of e-cigarettes not only via its coolness and minty flavour, but also by reducing the harshness from high concentrations of nicotine.	Randomised crossover trial
Riggare *et al.*[395] 2017	Benefit	The authors investigated the effectiveness of nicotine delivered through e-cigarettes for managing levodopa-induced dyskinesia, associated with Parkinson's disease, with nicotine The authors used the term 'patient-driven N-of-1' for self-tracking the effect, in this instance, managing levodopa-induced dyskinesia with nicotine. *Comparative groups*	Non-randomised before and after study

Author(s), year	Possible benefit or harm	Interventional trial papers on other outcomes	Trial design
		Comparison(s) of never-smoker (conventional combustible tobacco cigarette) using: (1) e-cigarette with nicotine 3 mg/ml (2) e-cigarette without nicotine The authors concluded that nicotine administered via e-cigarettes may have a reducing effect on levodopa-induced dyskinesia in individual patients with Parkinson's disease.	
Lee *et al.*[396] 2018	Harm	The authors reported on the **effects of second-hand exposure to nicotine from e-cigarettes.** *Comparative groups* Comparison(s) of never smokers (conventional combustible tobacco cigarette) with: (1) e-cigarette with 1.8% nicotine exposure sessions The authors concluded that there are cardiac autonomic effects of short-term second-hand exposure to nicotine from e-cigarette emissions in healthy non-smokers.	Randomised crossover trial
Melstrom *et al.* [397] 2018	Harm	The authors measured the **systemic absorption of nicotine following acute second-hand exposure to e-cigarette aerosol** in a realistic social setting. Never users of combustible tobacco products (never smoked more than 100 cigarettes in their lifetime), no use in the past year of non-combustible tobacco products (smokeless tobacco) or nicotine replacement therapies. Nonusers agreed to abstain from exposure to secondhand tobacco smoke or e-cigarette aerosol for 6 days before each exposure. *Comparative groups* The 3 e-cigarette users were the intervention itself. They vaped in front of the 3 never smokers who were the participants: The e-cigarettes used were: (1) iTaste variable voltage tank java with a mean nicotine content of 15.1 mg/ml (2) iTaste variable voltage tank swiss cherry with a mean nicotine content of 15.1 mg/ml (3) iTaste variable voltage tank peach with a mean nicotine content of 15.1 mg/ml (4) blu disposable e-cigarette classic tobacco with a mean nicotine content of 15.1 mg/ml (5) blu disposable e-cigarette cherry crush with a mean nicotine content of 15.1 mg/ml (6) Fling ice berry disposable e-cigarette with a mean nicotine content of 15.1 mg/ml (java, swiss cherry and peach) The authors concluded that although exposures may vary considerably, non-users can systemically absorb nicotine following acute exposure to second-hand e-cigarette aerosol.	Non-randomised before and after study
Walele Tanvir *et al.*[393] 2018	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **safety profile of Puritane™, a closed-system e-vapour product**, when used by smokers of conventional combustible tobacco cigarettes in a real-life setting over a 24-month period. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke between 5 and 30 tobacco cigarettes daily for ≥ 1 year) using: (1) Puritane, a closed system electronic vapour product (2) usual own brand conventional combustible tobacco cigarette The authors concluded that few serious adverse events, or withdrawals due to adverse events, occurred during the 24 months of Puritane™ use, none of which were related to use of the e-vaping product. The authors concluded that the use of the e-vaping product for up to 2 years in this study appears to be an acceptable alternative for smokers, with the advantage of reducing the exposure to potentially harmful smoke constituents.	Non-randomised trial

5 Findings: heat-not-burn harms and benefits

5.1 Introduction

We categorised the papers on the possible benefits and harms of heat-not-burn products according to epidemiological study design in order to assign a notional hierarchy of evidence to the literature. We firstly present descriptive studies (case series, case reports, and surveillance studies) that are deemed to provide the lowest level of epidemiological evidence. We then present observational studies (cross-sectional surveys, case-control studies, and longitudinal cohort studies), and end with interventional trials, that are deemed to provide the highest level of epidemiological evidence. The hierarchy of evidence does not include surveillance reports; additionally, only some of its depictions include cross-sectional surveys. However, we included these studies to present a comprehensive map of heat-not-burn products' harms and benefits. There were 28 peer-reviewed papers on the harms and benefits of heat-not-burn products; these comprised 2 case reports, 1 cross-sectional survey, and 25 interventional trials.

Within each study design, the possible benefits and harms outcomes that were identified through this mapping exercise are presented under nine headings. Seven of the headings were identified by the United States National Academies of Sciences, Engineering, and Medicine for classifying health research on tobacco products: (i) dependence and abuse liability; (ii) cardiovascular diseases; (iii) cancers; (iv) respiratory diseases; (v) oral diseases; (vi) developmental and reproductive effects; and (vii) injuries and poisonings. We added two further categories for outcomes that did not align with the Academies of Sciences' framework; these were: (viii) exposure to heat-not-burn toxins; and (ix) other outcomes.[6]

The heat-not-burn papers are categorised under the following adapted Academies of Sciences' umbrella terms: dependence and abuse liability (5 papers), cardiovascular diseases (8 papers), respiratory diseases (3 papers), and exposure to heat-not-burn toxins (12 papers). There are no peer-reviewed papers reporting on outcomes of cancers, oral diseases, developmental and reproductive effects, or injuries and poisonings. However, it should be noted that many of the papers grouped under the heading 'exposure to heat-not-burn toxins' report on outcomes which have been identified as definite or probable causes of a range of carcinogenic or neurological pathologies.

Summaries of the included heat-not-burn articles are presented in tables, which are organised by the nine outcome categories and by study design. We observed that the trial papers included in Section 5 of the report were written by either industry- or academic-based authors, and we have organised the tables to reflect the authors' place of work. In addition, we observed in several instances that the same lead trial author reported on studies employing a very similar design and frequently testing the same product, or a close variation of it, in different geographical populations. Therefore, in order to ensure a better understanding of the relationship pattern between the exposure and the outcome, the papers by the same team of authors are grouped by team, then by product, and then listed in chronological order.

The PRISMA flow chart for the mapping exercise is outlined in Figure 5.

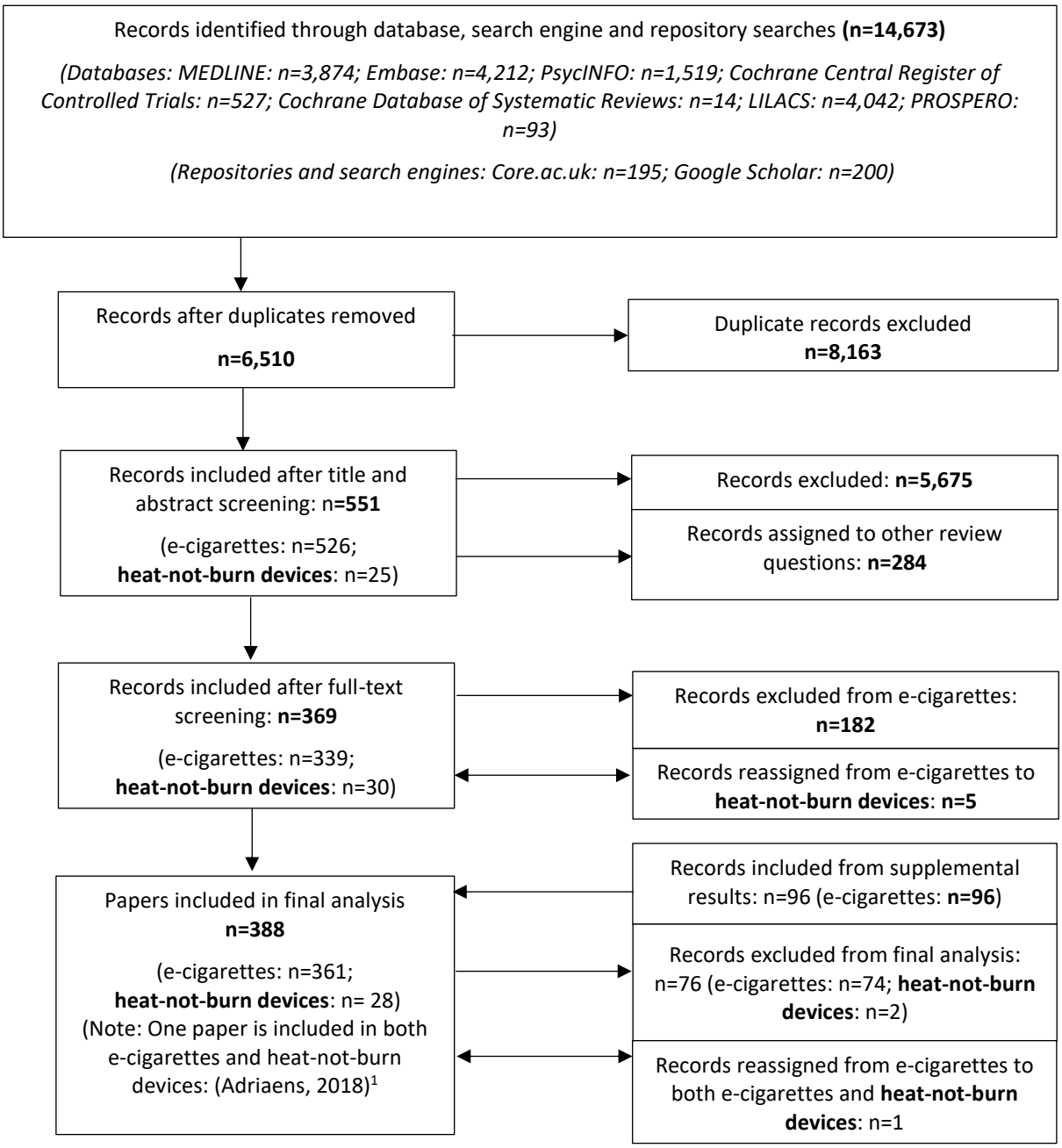


Figure 5 PRISMA flow chart

5.1.1 Outcomes assessed in the heat-not-burn papers

We categorised the papers' outcome indicators of harms or benefits of heat-not-burn products under the adapted Academies of Sciences framework headings. The indicators included psychological and physical measures of health and well-being. Broadly speaking, psychological measures were assessed using validated questionnaires. Biological measures were evaluated through assessment of organ and tissue functionality, or through other biological measures such as breath, blood, or urine levels of toxic or potentially toxic substances. The papers' authors reported toxic substances by acronym, the biomarker of exposure, or as a group titled 'harmful or potentially harmful smoke constituents'. We have reported the terms used by the papers' authors in the tabulated summaries. Some indicators did not exclusively align with individual adapted Academies of Sciences' umbrella terms. For example, measures of nicotine were regarded as indicators of dependence and abuse liability, but they also fitted under the umbrella term 'exposure to heat-not-burn toxins'. Similarly, assessments of organ and tissue functionality – for example, symptom-limited spiroergometry, which includes measures such as oxygen uptake – can be employed to assess aspects of both respiratory and cardiovascular function.

5.1.2 Harms or benefits

The principal focus of this mapping exercise was on mapping the harms and the benefits of heat-not-burn products. However, a determination of whether an outcome was considered a harm or a benefit was made by taking account of the relative or absolute nature of the relationship being examined. In other words, the effect of the heat-not-burn product(s) was assessed relative to whether the comparison group comprised non-smokers, smokers currently abstaining from smoking, smokers of conventional [combustible] tobacco cigarettes, vapers of e-cigarettes, or poly (or dual) users of two or more smoking-related products. For the trial papers, we have reported the authors' conclusions regarding their assessment of the effect of the heat-not-burn products on damage or injury to biological tissue, or on levels of toxicants measured. Therefore, in order to contextualise the harm or benefit of the reported exposure-outcome relationship, we have also provided details on the smoking and vaping behaviours of study participants with whom the comparisons have been made.

5.1.3 Paper characteristics

Possible harms and benefits associated with heat-not-burn products are reported in 28 peer-reviewed papers. Stratification by the research study design identified 2 case reports, 1 cross-sectional survey, and 25 interventional trials.

Five papers were authored by persons who were based in, or affiliated with, a university or hospital. Of these, two were case reports that presented findings on respiratory outcomes, one was a cross-sectional survey that reported on dependence and abuse liability, and two were interventional trials. One of these trials reported on dependence and abuse liability and the other reported on cardiovascular outcomes.

The remaining 23 papers were reporting the results of trials and authored by employees of the tobacco industry, including companies such as Philip Morris and Altria Client Services, R. J. Reynolds Tobacco Company, and Japan Tobacco International. Three papers were authored by Philip Morris employees, including employees with both tobacco industry and university affiliations. Industry-authored papers on trial results focused on the following areas: dependence and abuse liability, cardiovascular diseases, respiratory diseases, and exposure to heat-not-burn toxins. Several trial papers reported findings which could be placed under two or more umbrella terms (for example, 'cardiovascular diseases' and 'exposure to heat-not-burn toxins'). Where this occurred, papers were placed under the umbrella term that best reflected the principal focus of the trial.

Overall, outcomes were rarely clinical diseases or pathological features considered collectively to reflect the typical behaviour of a disease. A rare exception was the diagnosis of acute eosinophilic pneumonia in two case reports. More frequently, study outcomes represented a laboratory-based examination of body tissue to assess body system, organ, or tissue health or function, or toxicity levels – arising from the inhalation of chemical substances – in body fluids or breath.

5.2 Descriptive epidemiological studies: heat-not-burn products

We grouped three papers within this section: two case reports and one paper reporting findings from a cross-sectional survey. The authors of the case reports described two individual cases of hospital admissions due to adverse respiratory outcomes (specifically acute eosinophilic pneumonia). The cross-sectional survey reported on psychological measures of well-being – specifically perceived stress – in addition to other behavioural outcomes.

5.2.1 Case reports: heat-not-burn products

There were two case reports on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings. Both case reports described harms associated with respiratory disease outcomes (acute eosinophilic pneumonia) in young males living in Japan. One case occurred in 2016 and the other in 2018. Both cases recovered following hospital-based treatment.

5.2.1.1 Dependence and abuse liability: case reports

There were no case reports on the relationship between heat-not-burn products and dependence and abuse liability outcomes.

5.2.1.2 Cardiovascular diseases: case reports

There were no case reports on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.2.1.3 Cancers: case reports

There were no case reports on the relationship between heat-not-burn products and cancer outcomes.

5.2.1.4 Respiratory diseases: case reports

There were two case reports on the relationship between heat-not-burn products and respiratory disease outcomes (Table 53). Both case report papers described a diagnosis of acute eosinophilic pneumonia: one case occurred immediately after first use of a heat-not-burn product by a 16-year-old male,[398] and the other occurred after a 6-month period of use by a 20-year-old male.[399] Both cases recovered following hospital-based treatment. In both cases, the authors, who were clinical practitioners, concluded that the use of heat-not-burn products was the likely causal agent.

Table 53 Case reports on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Case reports on respiratory diseases, benefits or harms
Kamada *et al.* [399] 2016	Harm	Product: Unidentified device for smoking heat-not-burn cigarettes Dose taken or reported relevant behaviour: 20 heat-not-burn cigarettes per day over the previous 6 months, and who had recently purchased a second device for smoking heat-not-burn cigarettes. As a result of purchasing this second device, he had increased his smoking to 40 cigarettes per day 2 weeks Outcome: **Acute eosinophilic pneumonia**
Aokage *et al.* [398] 2018	Harm	Product: Heat-not-burn tobacco product Dose taken or reported relevant behaviour: First smoking heat-not-burn cigarettes Outcome: **Acute eosinophilic pneumonia**

5.2.1.5 Oral diseases: case reports

There were no case reports on the relationship between heat-not-burn products and oral disease outcomes.

5.2.1.6 Developmental and reproductive effects: case reports

There were no case reports on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.2.1.7 Injuries and poisonings: case reports

There were no case reports on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.2.1.8 Exposure to heat-not-burn toxins: case reports

There were no case reports on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.2.1.9 Other outcomes: case reports

There were no case reports on the relationship between heat-not-burn products and other outcomes.

5.2.2 Case series: heat-not-burn products

There were no case series papers on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings.

5.2.2.1 Dependence and abuse liability: case series

There were no case series papers on the relationship between heat-not-burn products and dependence and abuse liability outcomes.

5.2.2.2 Cardiovascular diseases: case series

There were no case series papers on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.2.2.3 Cancers: case series

There were no case series papers on the relationship between heat-not-burn products and cancer outcomes.

5.2.2.4 Respiratory diseases: case series papers

There were no case series papers on the relationship between heat-not-burn products and respiratory disease outcomes.

5.2.2.5 Oral diseases: case series

There were no case series papers on the relationship between heat-not-burn products and oral disease outcomes.

5.2.2.6 Developmental and reproductive effects: case series

There were no case series papers on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.2.2.7 Injuries and poisonings: case series

There were no case series papers on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.2.2.8 Exposure to heat-not-burn toxins: case series

There were no case series papers on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.2.2.9 Other outcomes: case series

There were no case series papers on the relationship between heat-not-burn products and other outcomes.

5.2.3 Information or surveillance system reports: heat-not-burn products

There were no information or surveillance systems papers on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings.

5.2.3.1 Dependence and abuse liability: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and dependence and abuse liability outcomes.

5.2.3.2 Cardiovascular diseases: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.2.3.3 Cancers: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and cancer outcomes.

5.2.3.4 Respiratory diseases: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and respiratory disease outcomes.

5.2.3.5 Oral diseases: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and oral disease outcomes.

5.2.3.6 Developmental and reproductive effects: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.2.3.7 Injuries and poisonings: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.2.3.8 Exposure to heat-not-burn toxins surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.2.3.9 Other outcomes: surveillance system reports

There were no information or surveillance systems papers on the relationship between heat-not-burn products and other outcomes.

5.3 Observational epidemiological studies: heat-not-burn products

5.3.1 Cross-sectional surveys: heat-not-burn products

There was one cross-sectional survey paper on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings. This was under the 'dependence and abuse liability' framework heading. The survey was completed in 2018 by 60,040 schoolchildren aged 12–18 years in South Korea, and was published in 2019. It examined the association of heat-not-burn tobacco products with perceived stress, frequency of physical activity, and Internet usage time, and the authors found an association between these variables

5.3.1.1 Dependence and abuse liability: cross-sectional surveys

There was one cross-sectional survey paper on the relationship between heat-not-burn products and dependence and abuse liability outcomes (Table 54). In the 2018 national survey of teenaged schoolchildren in South Korea, a series of questions on cigarettes, e-cigarettes, and heat-not-burn products were asked in order to assess the prevalence of use of these products and the factors associated with their use.[400] Using odds ratios, the authors measured the associations of perceived stress, and other behavioural outcomes such as frequency of physical activity, with use of a range of tobacco-related products, including heat-not-burn tobacco products. Of 60,040 teenaged schoolchildren, 50,778 (85%) reported never smoking, 7,694 (13%) used cigarettes or e-cigarettes alone or in combination, and the remaining 1,569 (3%) schoolchildren reported using a heat-not-burn tobacco product alone or in combination with other tobacco-related products. The odds of experiencing perceived stress was greater in users who reported simultaneous use of all tobacco-related products than in non-product users. With regard to perceived stress, frequency of physical activity, and Internet usage time, the authors reported that there were significant associations between high levels of perceived stress and cigarette-only use, dual use of cigarettes with e-cigarettes, and triple use of cigarettes with both e-cigarettes and heat-not-burn tobacco products. An association between higher heat-not-burn tobacco product use and higher perceived stress was reported. However, the cross-sectional nature of the findings prohibited assessment of a causal direction of the relationship; it simply indicated an association.

Table 54 Cross-sectional survey papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Cross-sectional survey papers on dependence and abuse liability
Lee *et al.* [400] 2019	Potential harm	The authors reported on current tobacco product use, including heat-not-burn tobacco products, in teenaged schoolchildren in South Korea and whether the use of heat-not-burn tobacco products is associated with perceived stress, frequency of physical activity, and Internet usage time. Age: 12–18 years. Sex: 30,463 males, 29,577 females. Country: South Korea Data source: Korean Youth Risk Behavior Web-based Survey Population size: 60,040 schoolchildren from a total of 800 schools (400 middle schools and 400 high schools) participated in the survey, which had a response rate of 95.6%. Data collection period: 2018 E-cigarettes, smoking, and other related status: The experience of the use of tobacco products during the participants' lifetime to evaluate the smoking patterns of adolescents was assessed through questionnaires. *Comparative exposure* (1) Never smoker or vaper (2) Conventional tobacco cigarette smoker only (3) E-cigarettes vaper only (4) Heat-not-burn tobacco products user only (5) Conventional combustible tobacco cigarettes and e-cigarettes dual user (6) Conventional combustible tobacco cigarettes and heat-not-burn tobacco products dual user (7) E-cigarettes and heat-not-burn tobacco products dual user (8) Conventional combustible tobacco cigarettes as well as e-cigarettes and heat-not-burn tobacco products dual user A single use of a tobacco product was defined as reporting the use of only one among the three tobacco products. Dual use refers to the use of two products. The tobacco ever use categories (and numbers of schoolchildren in each) were: never smoke (50,778); cigarettes only (4,690); e-cigarettes only (571); heat-not-burn tobacco products only (59); cigarettes and e-cigarettes (2,433); cigarettes and heat-not-burn tobacco products (147); e-cigarettes and heat-not-burn tobacco products (92); cigarettes as well as e-cigarettes and heat-not-burn tobacco products (1,270). Outcomes: The association of tobacco ever use with perceived stress and frequency of physical activity. Students with high perceived stress had higher odds of using cigarettes only, dual use of cigarettes and e-cigarettes, and triple use of cigarettes, e-cigarettes, and heat-not-burn tobacco products (odds ratio [OR]: 1.11, 1.17, and 1.34, respectively). Moderate perceived stress was negatively associated with the use of heat-not-burn tobacco products only compared to low perceived stress (OR: 0.47; 95% confidence interval [CI]: 0.24–0.93) and Internet usage time. The prevalence of lifetime heat-not-burn tobacco product use was 2.9%, including single use (0.1%), dual use (0.5%), and triple use (2.3%). The authors concluded that the findings indicated that adolescents with high perceived stress, a high frequency of physical activity, and who spent less time using the Internet were more likely to engage in the use of tobacco products. However, the strength and direction of the relationship varied according to smoking product type. Device and products: Not reported

5.3.1.2 Cardiovascular diseases: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.3.1.3 Cancers: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and cancer outcomes.

5.3.1.4 Respiratory diseases: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and respiratory disease outcomes.

5.3.1.5 Oral diseases: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and oral disease outcomes.

5.3.1.6 Developmental and reproductive effects: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.3.1.7 Injuries and poisonings: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.3.1.8 Exposure to heat-not-burn toxins: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.3.1.9 Other outcomes: cross-sectional surveys

There were no cross-sectional surveys on the relationship between heat-not-burn products and other outcomes.

5.3.2 Case-control studies: heat-not-burn products

There were no case-control studies on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings.

5.3.2.1 Dependence and abuse liability: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and dependence and abuse liability outcomes.

5.3.2.2 Cardiovascular diseases: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.3.2.3 Cancers: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and cancer outcomes.

5.3.2.4 Respiratory diseases: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and respiratory disease outcomes.

5.3.2.5 Oral diseases: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and oral disease outcomes.

5.3.2.6 Developmental and reproductive effects: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.3.2.7 Injuries and poisonings: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.3.2.8 Exposure to heat-not-burn toxins: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.3.2.9 Other outcomes: case-control studies

There were no case-control studies on the relationship between heat-not-burn products and other outcomes.

5.3.3 Longitudinal cohort studies: heat-not-burn products

There were no longitudinal cohort studies on the relationship between heat-not-burn products and any of the adapted Academies of Sciences' framework headings.

5.3.3.1 Dependence and abuse liability: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and dependence and abuse liability outcomes.

5.3.3.2 Cardiovascular diseases: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and cardiovascular disease outcomes.

5.3.3.3 Cancers: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and cancer outcomes.

5.3.3.4 Respiratory diseases: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and respiratory disease outcomes.

5.3.3.5 Oral diseases: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and oral disease outcomes.

5.3.3.6 Developmental and reproductive effects: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.3.3.7 Injuries and poisonings: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.3.3.8 Exposure to heat-not-burn toxins: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and exposure to heat-not-burn toxins outcomes.

5.3.3.9 Other outcomes: longitudinal cohort studies

There were no longitudinal cohort studies on the relationship between heat-not-burn products and other outcomes.

5.4 Interventional trials: heat-not-burn products

5.4.1 Study characterisation: heat-not-burn products

5.4.1.1 Trial design characteristics

There were 25 papers categorised as interventional trials (Tables 55–58). In these trials, participants were assigned to a heat-not-burn product(s) intervention, or control intervention(s), by the investigator. The investigator then measured the impact of the exposure on one or more outcomes at baseline and at subsequent timepoint(s). In general, in clinical laboratory-based trials, outcomes were assessed at specific timepoints and over a time range; in other words, data on exposure outcomes could be gathered near the timepoint of intervention, i.e. minutes or hours after intervention, and consecutively over several days. For example, data on nicotine levels (as its metabolite cotinine in blood) could be gathered 5 minutes post intervention, at four timepoints during each trial day, and for each day of the trial duration period. The laboratory trial papers included in our map of possible harms and benefits measured the acute impact of heat-not-burn product use on a range of outcomes within the time frame of the trials. Interventional trials allow quantification of the size and the direction of an intervention outcome effect. In the trial papers included in the map the time between assignment of the intervention and measurement of outcome(s) varied from hours to days. The interventional trial designs were controlled trials, and included randomised controlled trials and crossover trials. In the crossover trials, the participants were assigned to each of the interventions under investigation, often with a washout period before switching to the alternative intervention. Almost all trials were conducted in clinical laboratory settings following a standardised protocol of determining the device(s) and the heat-not-burn chemical compound(s) being assessed, and describing how to use the devices. This included issues such as tar and nicotine content, puffing frequency, and duration of exposure, along with how and when outcome measures were to be assessed.

5.4.1.2 Heat-not-burn products

There are different kinds of heat-not-burn tobacco products available, and the effect of each product varies. The authors reported on several products, and descriptions of three products are summarised in Sections 5.4.1.2.1, 5.4.1.2.2, and 5.4.1.2.3 in order to allow an understanding of the nature of products reported as part of the heat-not-burn mapping exercise. The products include, but are not limited to, the electrically heated cigarette smoking system (EHCSS), the tobacco heating system (THS), and the carbon-heated tobacco product prototype. More details on these products are available in the tables in Section 5.4.2.

5.4.1.2.1 Electrically heated cigarette smoking system products

The following examples of electrically heated cigarette smoking system products were identified in the interventional trial papers: the EHCSS series-K, EHCSS-K3, EHCSS-K6, EHCSS series-K lighter, and EHCSS series JLI.

Broadly, the products have been described by the trial authors as follows: the electrically heated cigarette smoking system consists of a cigarette containing a column of standard cigarette tobacco filler, wrapped in a tobacco mat with a paper overwrap, which is inserted into an e-cigarette lighter (or puff-activated lighter). The lighter's eight blades heat the cigarette only when the smoker takes a puff, thereby avoiding smouldering of the cigarette between puffs. Using this design, the tobacco reaches a peak temperature of approximately 500 °C during puffing. This contrasts with the burning cone of a lit-end the lit end of a conventional cigarette, which can reach approximately 900 °C during puffing. Some electrically heated cigarette smoking system devices differ in the construction of the filter, with later versions having a more efficient filter. The trial authors assessed that the more efficient filter results in reduced delivery of harmful or potentially harmful constituents in cigarette smoke when product versions were tested according to International Organization for Standardization methods. The electrically heated cigarette smoking system heater cannot be used to smoke conventional tobacco cigarettes. The third-generation EHCSS series-K puff-activated electrical heater can be used to smoke either non-menthol or menthol EHCSS series-K cigarettes.

It should be noted that the authors of some of the papers evaluating electrically heated cigarette smoking system heater products reported that the product being evaluated was not intended for sale on the market.

5.4.1.2.2 Tobacco heating system products

The following examples of tobacco heating system products were identified from the interventional trial papers: the THS 1.0, THS 2.1, and THS 2.2.

The trial authors reported that the tobacco heating system is made up of three components: the tobacco heating system tobacco stick, the holder, and the charger. The tobacco heating system tobacco stick has a tobacco plug containing processed tobacco cast leaf, which is covered by a paper wrap. The holder includes a battery, controlling electronics, and the heater element. The tobacco heating system tobacco stick is inserted into the holder and heats the tobacco via an electronically controlled heating blade. The charger recharges the holder. The tobacco heating system tobacco sticks are preheated for 30 seconds in the tobacco heating system holder, and the energy capacity of the holder is enough to maintain a product user session of 6 minutes. At the end of each product use session, the tobacco heating system holder requires recharging. The trial authors reported that the later versions of the tobacco heating system (THS 2.1 and THS 2.2) have evolved to become slimmer and less bulky than the THS 1.0, with the heating blade inserted directly into the tobacco heating system tobacco stick rather than heating the tobacco stick from the outside. This results in a more consistent heating of the tobacco at lower temperatures (<400 °C). Consequently, the trial authors reported that lower levels of harmful or potentially harmful smoke constituents were achieved in the THS 2.1 aerosol compared with the THS 1.0, as well as an improved sensorial experience, which addressed consumer feedback on the previous version. By design, the use of the THS 1.0 was limited to eight puffs per cigarette, while the THS 2.1 offers an operating window of 6 minutes and 14 puffs per cigarette, which is more in line with the smoking ritual observed with conventional tobacco cigarettes. The trial authors reported that the evolution of the electronic device from THS 1.0 to THS 2.1, in addition to lowering the operating temperature from 550 °C with the THS 1.0 to under 400 °C with the THS 2.1, decreased the emission of harmful or potentially harmful smoke constituents generated at temperatures above 400 °C. The trial authors concluded that the lowering of the operating temperature represented a significant improvement of the product. The heating of the tobacco heating system tobacco stick is initiated by pressing the button on the holder, and a light-emitting diode (LED) indicates when the initial heating process is complete. Like the third-generation electrically heated cigarette smoking system products, the tobacco heating system products were developed to smoke either non-menthol or menthol cigarettes.

5.4.1.2.3 Carbon-heated tobacco product

The trial authors reported that the carbon-heated tobacco product prototype MD2-E7 consists of a carbon heat source, a tobacco plug wrapped in paper, an empty tube (to allow aerosol transfer), and a filter (a strip of aluminium foil that attaches the carbon heat source to the tobacco plug). The trial authors stated that it looked like a conventional cigarette, and that the carbon-heated tobacco product was based on technology that avoided pyrolysis or combustion of tobacco. The heat-not-burn tobacco product prepared by Japan Tobacco International was described as an electrically heated cigarette consisting of four consecutive functional parts: a heat source assembly, comprising a carbon heat source; the film substrate, filled with tobacco leaf; a tobacco rod; and a filter. The trial authors stated that this makes the electrically heated cigarette structurally different from a conventional cigarette. After igniting the heat source assembly, a hot air flow generated by puffing warmed the film substrate and passed through the tobacco rod to generate smoke, and then the generated smoke was passed through a filter and inhaled by puffing.

5.4.1.2.4 Comparison of heat-not-burn products with conventional tobacco cigarettes

The trial authors provided some information on the chemical composition yield of heat-not-burn products and their comparison with conventional tobacco cigarettes. For example, the authors of one trial paper reported on the electrically heated cigarette smoking system compared with the conventional cigarette and found that the International Organization for Standardization yields for

the EHCSS-K3 were 3 mg tar, 0.2 mg nicotine, and 0.6 mg carbon monoxide, and for the EHCSS-K6 were 5 mg tar, 0.3 mg nicotine, and 0.6 mg carbon monoxide. These are lower than yields reported on the cigarette packaging for Marlboro (M6UK) (for which the yield was 6 mg tar, 0.5 mg nicotine, and 7 mg carbon monoxide), and lower than the carbon monoxide yield for Philip Morris One (PM1), which has 1 mg tar, 0.1 mg nicotine, and 2 mg carbon monoxide. The trial authors found that the carbon-heated tobacco product prototype MD2-E7 (which is another heat-not-burn product) yields were 3 mg tar, 2 mg glycerol, 0.4 mg nicotine, and 1 mg carbon monoxide.

5.4.1.3 Comparisons made in the heat-not-burn trial papers

In the 25 trials presented in Section 5.4.2, comparisons are made between the many smoking/vaping behavioural practices of the study population, as well as between various product types. In brief, comparisons of behaviours included contrasting between use of:

- Heat-not-burn products and e-cigarettes alone
- Heat-not-burn products, e-cigarettes, and conventional tobacco cigarettes
- Heat-not-burn products and conventional tobacco cigarettes
- Heat-not-burn products, conventional tobacco cigarettes, and smoking abstinence; and
- Conventional cigarette smokers and non-smokers at baseline.

The observed heterogeneity in comparison groups (i.e. non-smokers, smoking abstainers, smokers, e-cigarette users, and heat-not-burn users) was further compounded by assessment of a wide range of heat-not-burn products. These included: the electrically heated cigarette smoking system, the tobacco heating system, and other products such as the carbon-heated tobacco product prototype MD2-E7. In addition to the various heat-not-burn product types, various versions of the products were tested. For example, the EHCSS-K3 and EHCSS-K6 versions of an electrically heated cigarette smoking system, and the THS 2.1 and THS 2.2 versions of the tobacco heating system, were compared.

5.4.1.4 Study characteristics

The trials were completed on populations living in eight countries including Belgium (1 trial), Italy (1 trial), Japan (8 trials), Poland (3 trials), South Africa (3 trials), South Korea (1 trial), the UK (2 trials), and the USA (4 trials). Two trial papers did not report the country where it was based. The trial sample sizes ranged from 18 to 316. Twelve trials had fewer than 100 participants. The age range of trial participants was 19–65 years. Most trial participants were men. The trials were published between 2005 and 2019.

The number of interventional trial papers grouped by the adapted Academies of Sciences' framework headings were: 4 under dependence and abuse liability, 8 under cardiovascular diseases, 1 under respiratory diseases, and 12 under exposure to heat-not-burn toxins. There were no interventional trial papers under the following reporting areas: 'cancers', 'oral diseases', 'developmental and reproductive effects', 'injuries and poisonings', and other outcomes

5.4.2 Harms, harm reduction, and benefits: heat-not-burn products

The possible harms and benefit outcomes measured for heat-not-burn users under the 'dependence and abuse liability' heading included cigarette craving/urge to smoke, withdrawal symptoms, nicotine and its metabolites, and various forms of carbon monoxide. The outcomes measured under the 'cardiovascular diseases' heading included antioxidant status and oxidative stress, platelet activity, blood functions, endothelial function and dysfunction, lipid risk markers, cardiac risk markers, heart rate variability, cardiovascular risk and function, and factors related to oxygen uptake. The reported outcomes under the 'respiratory diseases' heading included measures of lung resistance, function, and volume. The outcomes measured under the 'exposure to heat-not-burn toxins' heading were an extensive array of harmful or potentially harmful constituents of tobacco smoke (see listing in Appendix 8).

Persons who abstained from smoking any products during the trial period had the best biomarkers of health when compared with those who used heat-not-burn products, vaped e-cigarettes, and/or smoked conventional tobacco cigarettes. The overarching conclusion by the trial authors was that heat-not-burn tobacco products had lower levels of the biomarkers, which are risk markers for adverse health outcomes, compared to levels observed in persons smoking conventional tobacco cigarettes.

5.4.2.1 Dependence and abuse liability: interventional trials

Four interventional trial papers reported the relationship between heat-not-burn products and dependence and abuse liability outcomes (Table 55 and Appendix 6). The authors of one trial, Adriaens *et al.* (2018), were university based;[1] the authors of the remaining three trials were industry based. The number of trial participants were 24, 28, 30, and 110. The duration of the trials varied according to the degree to which pre-data collection phase (to standardise behaviours and product use) was undertaken; the pre-data collection period ranged from 3 to 8 days. However, the actual period over which data assessing the effect of the intervention were collected ranged from 2 to 5 days, which illustrates the short-term nature of the intervention and measurement process. The outcomes included, but were not limited to:

- Cigarette craving/urge to smoke
- Withdrawal symptoms
- Urine nicotine, its metabolites, and nicotine concentration curves
- Exhaled carbon monoxide and carboxyhaemoglobin, and
- Cough assessment.

Other outcomes reported in these papers included product evaluation, participants' product preferences, and the assessment of adverse events (respiratory symptoms such as cough assessment; changes in vital signs; body mass index; spirometry findings; electrocardiography; clinical chemistry; haematology; urinalysis; and physical examinations).

Roethig *et al.*[401] (2005) reported findings from 110 participants in a controlled, parallel-group design trial with forced switching. Here, two electrically heated cigarette smoking systems (first-generation EHCSS1 and EHCSS2), two forms of conventional tobacco cigarettes (CC1 and CC2), and a smoking abstinence group were assessed over 3 days. The authors measured several biomarkers of exposure under controlled smoking conditions and reported that lowering the temperature during tobacco combustion resulted in a substantial reduction in exposure to carbon monoxide, carboxyhaemoglobin, and nicotine and urine mutagenicity (specifically urine nicotine and five of its metabolites) in those using the EHCSS1 and EHCSS2 devices when compared to exposures in persons using conventional tobacco cigarettes.

The other three papers reported on findings from open-label randomised trials. Picavet *et al*.[402] (2016) reported findings from 28 participants participating in a 2-day, two-period, two-sequence crossover study. The authors assessed outcomes after single and ad libitum use of the THS 2.1 or conventional tobacco cigarettes. The authors concluded that the THS 2.1 effectively delivered nicotine and achieved similar pharmacokinetic profiles (measured as nicotine blood levels) as conventional tobacco cigarettes while reducing the urge to smoke. Adriaens *et al.*[1] (2018) reported findings from 30 subjects who participated in a 3-day randomised crossover trial evaluating cigarette craving, withdrawal symptoms, and exhaled carbon monoxide among users of the heat-not-burn product IQOS™, e-cigarette users, and conventional cigarette users. The authors concluded that cravings were reduced in the heat-not-burn product users following short-term use. Yuki *et al*.[386] (2017) reported findings from 24 participants participating in a 3-day, two-period, two-sequence crossover study. The authors assessed outcomes after use of a prototype novel tobacco vapour product or conventional tobacco cigarettes. The authors concluded that the pharmacokinetics of nicotine following prototype novel tobacco vapour product use were not markedly different from those following conventional cigarette use, while the prototype novel tobacco vapour product provided less nicotine following a controlled single use.

Table 55 Interventional trial papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		Industry-based trials	
Roethig *et al.* [401] 2005	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of carbon monoxide, carboxyhaemoglobin, nicotine, and urine mutagenicity (specifically urine nicotine and five of its metabolites** (nicotine-N-glucuronide, cotinine, cotinine-N-glucuronide, trans-3'-hydroxycotinine, and trans-3'-hydroxycotinine-O-glucuronide)) in conventional combustible tobacco cigarette brand users, electrically heated cigarette smoking system users, and low-tar conventional combustible tobacco cigarette users. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke between 5 and 25 Marlboro Lights per day at baseline) using: (1) electrically heated cigarette smoking system (EHCSS 1) (2) electrically heated cigarette smoking system (EHCSS 2) (3) no smoking (4) low-tar combustible conventional cigarette (Marlboro Ultra) The authors concluded that lowering the temperature during tobacco combustion results in a substantial reduction in exposure to the smoke constituents measured.	Randomised crossover trial
Picavet *et al.* [402] 2016	Equal harm to conventional combustible tobacco cigarettes	The authors reported on the **relationship between use of the THS 2.1 or conventional combustible tobacco cigarettes, and the pharmacokinetics of nicotine,** specifically a range of mean nicotine concentration curves. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 10 commercially available non-menthol cigarettes per day for ≥ 4 weeks, with ≤1 mg nicotine per cigarette, at baseline) with: (1) Tobacco Heating System 2.1 (THS 2.1) The authors concluded that the THS 2.1 effectively delivers nicotine and achieves similar pharmacokinetic profiles as conventional combustible tobacco cigarettes. The THS 2.1 also reduced the urge to smoke to a similar degree as conventional combustible tobacco cigarettes.	Randomised crossover trial
Yuki *et al.* [386] 2017	Equal harm to conventional combustible tobacco cigarettes	The authors reported on **the pharmacokinetics of nicotine following the use of a prototype novel tobacco vapour product in comparison to a conventional combustible tobacco cigarette.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥11 tobacco cigarettes per day for ≥ 1 year at baseline) using: (1) prototype novel tobacco vapor product (2) conventional cigarette The authors concluded that under the conditions of the present study, the pharmacokinetics of nicotine following prototype novel tobacco vapour product use were not markedly different from those following conventional combustible tobacco cigarette use, while the prototype novel tobacco vapour product provided less nicotine following a controlled single use.	Randomised crossover trial
		University-based trials	
Adriaens *et al.* [1] 2018	Beneficial compared with combustible tobacco cigarettes	The authors reported on a 3-day randomised crossover trial, focusing on the **behavioural and experiential effects of the short-term use of the heat-not-burn product IQOS™**, versus an e-cigarette and versus a conventional combustible tobacco cigarette, in current smokers who were novice users of both	Non-randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability	Trial design
		IQOS™ and of e-cigarettes. The purpose was to investigate the effect of using IQOS™ on exhaled carbon monoxide, **acute cigarette craving, withdrawal symptoms, and subjective positive and negative experiences** after overnight smoking abstinence, compared to using an e-cigarette or a conventional combustible tobacco cigarette, and to investigate which product (the e-cigarette or IQOS™) would be preferred. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (≥10 cigarettes per day for ≥ 3 years and no intention to quit at baseline) using: (1) a regular tobacco cigarette, (2) an e-cigarette (3) the IQOSTM HnB tobacco product The authors concluded that short-term use of a specific heat-not-burn product, IQOS™, can be effective in momentarily reducing acute conventional combustible tobacco cigarette craving and withdrawal symptoms, while having a minimal impact on exhaled carbon monoxide levels and being slightly more liked by novice users than an e-cigarette. They stated, however, that this does not guarantee that craving/withdrawal symptom reduction will also be sustained over longer time spans or in cases of repeated use, nor do they provide assurance that these effects are sufficient to lead to smoking reduction or cessation in smokers willing to quit or cut down on conventional combustible tobacco cigarettes.	

5.4.2.2 Cardiovascular diseases: interventional trials

Eight interventional trial papers reported on the relationship between heat-not-burn products and a range of cardiovascular disease risk markers (Table 56 and Appendix 6). Risk markers included indicators of oxidative stress, damage and inflammation, endothelial dysfunction, coagulation, heart function, measures of metabolic syndrome, and indicators of a hypercoagulable state. An overview of the study characteristics of cardiovascular-related measures, trial design, sample size, and specifics on intervention devices and products is provided here, with more detail reported in Table 56. The toxins reported included measures of toxic gases (such as carbon monoxide and biomarkers of nicotine exposure). More specific examples of the cardiovascular (and toxin) outcomes included, but were not limited to:

- Antioxidant status and oxidative stress: levels of vitamin E and serum hydrogen peroxide (H_2O_2) breakdown activity, and 8-epi-prostaglandin F2α (8-epi-PGF2α)
- Oxidative damage and inflammation: isoprostane, isomers and metabolites iPF2a-III, 2,3-di-noriPF2a- III, iPF2a-VI, 8,12-isoiPF2a- VI, and PGF2a
- Platelet activation/activity: soluble CD40 ligand (sCD40L) and soluble P-selectin, and 11-DTXB2
- Endothelial dysfunction/function: flow-mediated dilation, and soluble intracellular adhesion molecule-1 (sICAM-1)
- Lipid metabolism: high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and total cholesterol
- Specific markers of inflammation: total white blood cells (WBC), soluble intercellular adhesion molecule-1 (sICAM-1), C-reactive protein
- Cardiovascular risk/function: homocysteine, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and blood pressure (systolic, diastolic)
- Metabolic syndrome, including insulin resistance: blood glucose, haemoglobin A1c (HbA1c), body weight, and waist circumference

- Serum levels of soluble NOX2-derived peptide, a marker of NADPH (nicotinamide adenine dinucleotide phosphate oxidase) oxidase activation
- Heart rate variability derived from the 24-hour electrocardiogram: NN interval (i.e. normal-to-normal heart beat interval), SDNN (i.e. standard deviation of all NN intervals), SDANN (i.e. standard deviation of all 5-minute averaged normal-to-normal heart beat interval), NN intervals in a 24-hour period, and the square root of the mean of all squared differences between adjacent NN intervals in a 24-hour period
- Hypercoagulable state: fibrinogen, homocysteine, hematocrit, haemoglobin (HgB), and platelets
- Lipid/cardiac risk markers: high-density lipoprotein (HDL), low-density lipoprotein (LDL), HDL/LDL ratio, oxidised LDL (OxLDL), and triglycerides
- Endothelial function: circulating endothelial precursor (CEP) cells
- DNA damage: sister chromatid exchange (SCE) in peripheral lymphocytes
- Full blood cell count, serum nicotine and cotinine
- Symptom-limited spiroergometry (spiroergometric parameters included oxygen uptake, carbon monoxide exhalation, heart rate, and systolic and diastolic blood pressure 12-lead electrocardiogram)
- Blood carboxyhaemoglobin (COHb), nitric oxide (NO), and concentrations of thiocyanate (plasma SCN) a biomarker of exposure for hydrogen cyanide
- Nicotine and five major metabolites (nicotineglucuronide, cotinine and its glucuronide, trans-3'-hydroxycotinine and its glucuronide)
- Cigarette smoke constituents (biomarkers of exposure): NNK (3-hydroxy-1-methylpropyl-mercapturic acid), 4-ABP (4-ABP: 4-aminobiphenyl), pyrene (PAH: polycyclic aromatic hydrocarbon) (1-OHP: 1-hydroxypyrene), benzene, 1,3-butadiene (MHBMA: monohydroxybutenyl mercapturic acid), acrolein (3-HPMA: 3-hydroxypropylmercapturic acid)
- Adenosine diphosphate (ADP)-induced platelet aggregation, and 8-epi-PGF2α; and
- 11-dehydro-thromboxane B2 (11-DTXB2).

The authors of one paper reporting on outcomes for cardiovascular disease, Biondi-Zoccai *et al.*[22] (2019), were university based, while the authors of the remaining papers were employees of Philip Morris, R. J. Reynolds Tobacco Company, or Japan Tobacco International. The trial from Biondi-Zoccai *et al.* is reported first, followed by the remaining seven trials, which are listed chronologically, and those published within the same year are listed alphabetically by the first author's name.

Biondi-Zoccai *et al.*[22] (2019) conducted a randomised crossover study over 4 weeks on 20 subjects. Participants were allocated to six different cycles undertaking a single use of each product: a heat-not-burn cigarette, an e-cigarette, and a conventional cigarette. The 20 participants underwent a 1-week washout period between exposures. Participants used all three products assessed in the trial. Outcomes of oxidative stress, antioxidant reserve, platelet activation, flow-mediated dilation, blood pressure, and satisfaction scores show adverse effects following a single use of each product. However, the adverse effects observed for measures of oxidative activation (NOX2-derived peptide) and potent agonists of platelet and vascular thromboxane 8-isoprostaglandin vitamin E) following use of the new-generation heat-not-burn cigarette were less extreme than those observed following use of the other products. The effects of heat-not-burn cigarettes and e-cigarettes on flow-mediated dilation (soluble CD40 ligand and soluble P-selectin) were less damaging than that of the conventional tobacco cigarettes. The heat-not-burn cigarette, and, to a lesser extent, the e-cigarette, exhibited lower impacts on raising blood pressure than the conventional tobacco cigarettes.

The remaining seven trials were by industry-based authors and included some form of randomisation. In many, control was achieved by a crossover study design, where findings were assessed in the same individuals at different timepoints and following exposure to the different interventions. In some trials, a washout period between exposures was reported. Some trials were conducted where individuals were allocated to one intervention only. These randomised controlled trials without crossover consisted of two or three study arms. Most trials were open-label (that is, neither the

participants nor the investigators were blinded to the intervention(s)). In crossover trials, the number of periods from which outcomes were assessed ranged from two to four. In several cases, the trial period was preceded by a preparatory period of up to 40 days, wherein participants were instructed in standardised behavioural regimes, including dietary intake and product use. In two trials, a subsequent follow-up period of up to 80 days was undertaken in order to assess the incidence of adverse events post exposure.

The data collection period assessing the exposure-outcome relationship varied. In five of the six trials conducted by Philip Morris data were gathered over 3 to 5 days; in the sixth trial data were gathered over a 12-month period. The R. J. Reynolds Tobacco Company trial gathered data over a 24-week period. Reported outcomes reflected outcomes gathered during these quantified periods. Trials were mainly conducted in a controlled situation with trained observers.

The number of participants in the industry-based trials ranged from 18 to 316. The six Philip Morris trials were conducted in Japan, South Africa (two trials), Poland, the USA and at one unidentified location. Participants numbered: 316 (Poland), 160 (Japan), 82 (USA), 34 (unidentified location), and 18 (in both South Africa trials). The R. J. Reynolds Tobacco Company trial in the USA consisted of 150 participants

Unverdorben *et al*. [403] (2007) reported on improved exercise performance assessed by symptom-limited spiroergometry parameters in 18 study participants. They found that persons who did not smoke or who used second-generation electrically heated cigarette smoking systems showed improved outcome measures relative to conventional cigarette users. A second paper by Unverdorben *et al*.[404] (2008), on 18 participants in a crossover trial that switched between three interventions (smoking conventional tobacco cigarettes, using an electrically heated cigarette smoking system, or smoking abstinence) over a 7-day period, found improvements in heart rate and rate-pressure-product parameters in persons switching to an electrically heated cigarette smoking system, and noted even greater improvements in participants who stopped smoking.

Roethig *et al*[405] analysed a range of biomarkers of tobacco smoke exposure and cardiovascular risk factors in 97 tobacco cigarette smokers who were either switched to a second-generation electrically heated cigarette smoking system or continued smoking conventional tobacco cigarettes for 12 months following baseline measurements. The authors concluded that there was a rapid and sustained reduction in all biomarkers of exposure after switching to the electronic heated cigarette smoking system, with statistically significant reductions in several cardiovascular risk factors from the baseline levels.

Munjal *et al.*[406] (2009) measured heart rate variability in 30 of 34 participants randomly assigned to either a conventional cigarette or an electrically heated cigarette smoking system over a 3-day trial period. The authors concluded that after 3 days, adult smokers tended to show increased heart rate variability with reduced exposure to conventional cigarette smoke, indicating a physiologically favourable change in the autonomous nervous system.+ However, it should be noted that the heat-not-burn device was solely a research tool and was not commercially available.

Martin Leroy *et al.*[407] (2012) reported a per-protocol analysis at 8 weeks, including 309 of 316 study participants, which measured blood health biomarkers and selected harmful and potentially harmful constituents of tobacco in two study groups (EHCSS-K6 users, and conventional cigarette users). The findings indicated an increase in high-density lipoprotein (HDL) cholesterol, and reductions in red blood cell count, haemoglobin, and haematocrit levels in the EHCSS-K6 group. All biomarkers of exposure to the selected harmful and potentially harmful constituents in conventional cigarette smoke decreased in the EHCSS-K6 group, despite an increase in EHCSS-K6 cigarette consumption, when compared to the conventional cigarette group. A list of harmful and potentially harmful constituents is presented in Appendix 8.

Ogden *et al* [408] (2015) measured oxidative damage, lipids, indicators of a hypercoagulable state, insulin resistance, endothelial function, and DNA damage in a 24-week trial of 150 smokers randomised to use of tobacco-heating systems, snus, or ultra-low machine yield tobacco-burning cigarettes. The authors reported improvements in some but not all biomarkers for each of the three products assessed relative to values among conventional cigarette users. They also reported that

consistent and statistically significant differences in pairwise comparisons between product groups were not observed.

Lüdicke *et al*.[409] (2018) reported findings for 104 of 160 trial participants in Japan who switched from conventional tobacco cigarettes to the menthol THS 2.2, assessing a range of outcomes including oxidative stress, endothelial function, lipid metabolism, cardiovascular risk/function (including systolic and diastolic blood pressure), and measures of metabolic syndrome. The authors concluded that switching from conventional tobacco cigarettes to the menthol THS 2.2 was associated with reductions in biomarkers of exposure to conventional cigarette smoke, and changes were observed in clinically relevant biomarkers of oxidative stress (8-epi-prostaglandin F2α), platelet activity (11-dehydro-thromboxane B2), endothelial function (soluble intracellular adhesion molecule-1), lipid metabolism (high-density lipoprotein (HDL) cholesterol), and lung function (forced expiratory volume in 1 second) that were similar to the smoking abstinence group.

Table 56 Interventional trial papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		University-based trials	
Biondi-Zoccai *et al.* [22] 2019	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **acute effects of a single use of heat-not-burn cigarettes**, electronic vaping cigarettes, and conventional combustible tobacco cigarettes in healthy smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (mean years smoking: 15±SD 12 at baseline) using: (1) heat-not-burn cigarettes (2) e-cigarettes (3) conventional combustible tobacco cigarettes The authors concluded that the acute effects of heat-not-burn cigarettes, electronic vaping cigarettes, and conventional combustible tobacco cigarettes are different on several oxidative stress, antioxidant reserve, platelet function, cardiovascular, and satisfaction dimensions, with conventional combustible tobacco cigarettes showing the most detrimental changes in clinically relevant features, thus suggesting that these modified-risk products may prove useful as tools to quit smoking conventional combustible tobacco cigarettes.	Randomised crossover trial
		Industry-based trials	
Unverdorben *et al.* [403] 2007	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **exercise performance following reduced exposure to conventional combustible tobacco cigarette smoke** and no smoking in adult smokers switching from conventional combustible tobacco cigarettes to an electrically heated cigarette smoking system or smoking abstinence. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes per day for ≥10 years, with brand and cigarettes per day stable for ≥3 months, at baseline) with: (1) conventional combustible tobacco cigarette (2) second-generation EHCSS series JLI They found that persons who did not smoke or who used second-generation electrically heated cigarette smoking systems showed improved outcome measures relative to conventional combustible tobacco cigarette users.	Randomised crossover trial
Unverdorben *et al.* [404] 2008	Less harmful than conventional combustib	The authors reported on the **prognostic parameters of heart rate (HR) and rate-pressure-product (RPP)** on exercise performance in adult smokers switching from a conventional combustible tobacco cigarette to a potential exposure-reduced electrically heated cigarette smoking system or to no smoking.	Randomised crossover trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
	le tobacco cigarettes	*Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes per day for ≥10 years, with brand and cigarettes per day stable for ≥3 months, at baseline) with: (1) "Controlled smoking" conditions (2) EHCSS smoking system (EHCSS series JLI (3) conventional combustible tobacco cigarette The authors concluded that reduced exposure to tobacco smoke or not smoking for 3 days may translate into improvements in heart rate and rate-pressure-product parameters that are associated with cardiovascular prognosis. These improvements seem to be more pronounced during smoking abstinence than during the use of the reduced-exposure product, suggesting a dose-dependent trend.	
Roethig *et al*[405] 2008	Less harmful than tobacco cigarettes	Authors reported on **cardiovascular risk factors in adults' smokers switching from conventional tobacco cigarettes to a second-generation electronic heated cigarette smoking system** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes, with 1–7 mg tar, per day for ≥10 years, with brand and cigarettes per day stable for ≥3 months, at baseline) using: (1) EHCSS1 (Accord first-generation EHCSS series E4) (2) EHCSS2 (Oasis first-generation EHCSS series E4) (3) conventional cigarette brand (CC1, Marlboro Lights) (4) low-tar conventional cigarette (CC2, Marlboro Ultra) The authors concluded that there was a rapid and sustained reduction in all biomarkers of exposure after switching to the electronic heated cigarette smoking system, with statistically significant reductions from baseline	Randomised crossover trial
Munjal *et al.* [406] 2009	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **heart rate variability** among users of different tobacco products. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes per day for ≥10 years at baseline) using: (1) conventional cigarette (2) third generation, electrically heated cigarette smoking system (EHCSS series K) The authors concluded that adult smokers tend to show increased heart rate variability with reduced exposure to conventional combustible tobacco cigarette smoke after 3 days, indicating a physiologically favourable change in the autonomous nervous system.	Randomised crossover trial
Martin Leroy *et al.* [407] 2012	Equal harm to conventional combustible tobacco cigarettes in some measures Less harmful than conventional combustib	The authors reported on **biomarkers associated with cardiovascular risk and biomarkers of exposure to 10 selected harmful and potentially harmful constituents** in conventional combustible tobacco cigarette smoke, comparing findings with those smoking the the EHCSS-K6. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes, with 3–10 mg tar, per day for ≥10 years at baseline) using: (1) EHCSS-K6 (2) conventional tobacco cigarettes The authors concluded that there were no statistically significant differences in the two primary biomarkers between the study groups at the end of the study. End-of-study comparisons of secondary biomarkers between study groups indicated an increase in high-density lipoprotein (HDL) cholesterol, and reductions in red	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
	le tobacco cigarettes for other measures	blood cell count, haemoglobin, and haematocrit levels in the EHCSS-K6 group. All biomarkers of exposure to the selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke were decreased in the EHCSS-K6 group, despite an increase in product consumption, compared to the levels found in the conventional combustible tobacco cigarette group. There were no apparent differences in any of the safety assessment parameters between the groups, and the overall incidence of study-related adverse events was low.	
Ogden *et al.* [408] 2015	Equal harm to conventional combustible tobacco cigarettes	The authors reported on changes in **biomarkers of biological effect among adult conventional combustible tobacco cigarette smokers who switched to tobacco-heating systems, snus, or ultra-low machine yield tobacco-burning cigarettes for 24 weeks**. Comparisons were made between smokers and a group of never-smokers at baseline, and among the three tobacco-using groups over time and in comparison, with each other. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (exclusive for 6 months, ≥15 cigarettes per day for ≥10 years and did not intend to quit at baseline) using: (1) tobacco-heating cigarette (Eclipse brand cigarette, non-menthol (2) tobacco-heating cigarette (Eclipse brand cigarette, menthol (3) snus (Camel SNUS, subject choice of Frost, Spice and Mellow varieties) (4) an ultra-low machine yield tobacco-burning cigarette (5) Cambridge Filter Method ''tar'' Camel non-menthol or Salem, (6) Cambridge Filter Method ''tar'' menthol (7) never smokers (baseline comparison) The authors concluded that half of the biomarkers of biological effect evaluated were statistically significantly different in the baseline comparisons between smokers and never-smokers. Differences in C-reactive proteins, high-density lipoproteins (HDL), low-density lipoproteins (LDL), HDL/LDL, triglycerides, fibrinogen, and platelets between smokers and non-smokers, were not observed in this study. They noted that consistent and statistically significant differences in pairwise comparisons between product groups were not observed.	Randomised controlled trial
Lüdicke *et al.* [409] 2018a	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **risk profile of a new tobacco product**, the menthol THS 2.2, an alternative to conventional combustible tobacco cigarettes. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥10 menthol cigarettes per day, with ≤1 mg of nicotine, for the previous 4 weeks, and had smoked for ≥3 years with no plan to quit at baseline) using: (1) menthol Tobacco Heating System 2.2 (mTHS) (2) conventional combustible tobacco cigarette (3) smoking abstinence The authors concluded that switching from conventional combustible tobacco cigarettes to the menthol THS 2.2 was associated with reductions in biomarkers of exposure to conventional combustible tobacco cigarette smoke, and changes were observed in clinically relevant biomarkers of oxidative stress (8-epi-prostaglandin F2α), platelet activity (11-dehydro-thromboxane B2), endothelial function (soluble intracellular adhesion molecule-1), lipid metabolism (high-density lipoprotein (HDL) cholesterol), and lung function (forced expiratory volume in 1 second) which were similar to the smoking abstinent group. The results suggest that switching to the menthol THS 2.2 has	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases	Trial design
		the potential to reduce the adverse health effects of using conventional combustible tobacco cigarettes.	

5.4.2.3 Cancers: interventional trials

There were no interventional trials on the relationship between heat-not-burn products and cancer outcomes.

5.4.2.4 Respiratory diseases: interventional trials

There was one interventional trial on the relationship between heat-not-burn products and respiratory disease outcomes (Table 57 and Appendix 6). The trial's reported respiratory outcomes included the following measures of lung resistance, function, and volume:

- Airway resistance – measured by specific airway conductance, airway conductance, specific resistance, and raw resistance
- Spirometry – measured by forced expiratory volume after 1 second, forced expiratory flow after the first 25% of the vital capacity, forced expiratory flow after the first 50% of the vital capacity, forced mid-expiratory flow, peak expiratory flow, and peak inspiratory flow; and
- Lung volumes – measured by vital capacity, forced inspiratory vital capacity, and thoracic gas volume.
- Respiratory rate, tidal volume, and expiratory time

Unverdorben *et al.*[410] (2010) reported on respiratory outcomes from a single-blind (technicians and laboratory staff), randomised, controlled, three-period crossover study with 49 male participants. The intervention was conducted over 3 days. Comparisons were made between outcomes following conventional cigarette use, third-generation electrically heated cigarette smoking system use, and smoking abstinence. The authors concluded that acute and reversible effects of different cigarette smoke exposures and no smoking on mid- to small-size pulmonary airways occurs in a dose-dependent manner, with the damage occurring in a decreasing stepwise manner from conventional cigarette users, to third-generation electrically heated cigarette smoking system users, to the least damage in smoking abstainers.

Table 57 Interventional trial papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases	Study design
		Industry-based trials	
Unverdorben *et al.* [410] 2010	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the extent and potential **reversibility of changes in pulmonary function** in adult smokers of conventional combustible tobacco cigarettes after 3 days of either smoking conventional combustible tobacco cigarettes, using an electrically heated cigarette smoking system, or smoking abstinence. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 20 to 40 cigarettes per day for ≥10 years, with brand and cigarettes per day stable for ≥3 months, at baseline) with: (1) conventional cigarette (2) electrically heated smoking system (EHCSS series K) (3) did not smoke Characteristics of baseline group: (1) conventional combustible tobacco cigarette users The authors concluded that acute and reversible effects of different cigarette smoke exposures and no smoking on mid- to small-size pulmonary airways occurs in a dose-dependent manner.	Randomised crossover trial

5.4.2.5 Oral diseases: interventional trials

There were no interventional trials on the relationship between heat-not-burn products and oral disease outcomes.

5.4.2.6 Developmental and reproductive effects: interventional trials

There were no interventional trials on the relationship between heat-not-burn products and developmental and reproductive effects outcomes.

5.4.2.7 Injuries and poisonings: interventional trials

There were no interventional trials on the relationship between heat-not-burn products and injuries and poisonings outcomes.

5.4.2.8 Exposure to heat-not-burn toxins: interventional trials

There were 12 interventional trial papers reporting on the relationship between heat-not-burn products and toxin-related outcomes (Table 58 and Appendix 6). The intervention portions of the trials were short term, usually of 2–3 days' duration, but an intervention assessment period of up to 4 weeks was reported. In some studies, a pre-trial monitoring period of between 7 and 40 days was conducted. During this time, participants were instructed to undertake standardised dietary and lifestyle behaviours, including protocol-agreed smoking-related behaviours. A post-trial period of between 7 and 80 days, where participants were asked about subsequent effects or any adverse events, was also conducted in a small number of trials.

All interventional trial papers except for one provided information on the chemical composition of the intervention. From the reported data, it was clear that the term 'heat-not-burn products' was an umbrella term for a range of products which shared specific characteristics but also exhibited differences regarding features such as nicotine strength; glycerine, glycerol, and tar content; flavourings; and heating temperature. Different generations of heat-not-burn products, heat-not-burn products with and without menthol, and carbon-heated tobacco products were assessed. Comparisons were made between a range of conventional tobacco cigarettes with and without menthol. In addition, some studies' outcomes were contrasted not only in persons who were randomised to using a heat-not-burn product or a conventional cigarette, but also with persons randomised to abstain from smoking during the trial period. Hence, two-, three-, or four-way comparisons of heat-not-burn, conventional tobacco cigarettes, and smoking abstention were reported.

Examples of heat-not-burn products studied included, but were not limited to, the following:

- A 7 mg/cigarette (according to International Organization for Standardization conditions) tar combustible tobacco non-menthol cigarette, the glo™ THP 1.0 with non-menthol NeoStiks, or the menthol-containing cigarette equivalent, the glo™ THP 1.0 with menthol NeoStiks
- The heat-not-burn THS 2.2 test product, containing 0.5 mg nicotine (as determined under International Organization for Standardization conditions) and 56.4 mg/stick of glycerine, or the menthol-containing equivalent, the menthol THS 2.2; and
- The carbon-heated tobacco product prototype MD2-E7, containing 3 mg tar, 2 mg glycerol, and 0.4 mg nicotine, and with a 1 mg carbon monoxide (CO) yield.

Each of these products was compared with a nationally available cigarette brand from the country in which the study was being conducted with varying values of reported tar and nicotine content. For example, packaging of a conventional tobacco cigarette in one of the studies conducted in Japan reported 10 mg tar and 0.8 mg nicotine in the conventional cigarette. Alternatively, in other studies, participants supplied their own conventional tobacco cigarettes, the chemical composition of which was not documented. The study countries were Japan, Poland, the UK, and the USA.

A wide range of potentially harmful constituents, biomarkers, and/or toxins; known risk markers; or causal factors in the development of a range of diseases were measured. Below we have listed toxins

using the nomenclatures as reported in the individual papers. Where possible we have expanded the abbreviations employed in tables within the papers using the details provide at the end of the reporting table or within the body of the text. However, on a small number of occasions the papers authors did not provide a more complete name. We have not extrapolated beyond the reporting authors text. Some toxins have been classified as Group 1 (the agent is carcinogenic to humans), Group 2A (the agent is probably carcinogenic to humans), or Group 2B (the agent is possibly carcinogenic to humans) by the International Agency for Research on Cancer.[411] The toxins drive metabolic activation that results in a range of pathogenic changes, including, but not limited to: binding of reactive metabolites to DNA and proteins, mutagenicity, oxidative DNA damage, chromosomal damage, and cytotoxicity. Many of the toxins have been identified as determinants in the development of lung and bladder cancers, or potential severe neurological harm. However, it should be noted that the clinical consequences of their presence in human body tissue in these trials requires a longer follow-up time period in order to more fully assess their effect.

The most common toxin outcomes assessed in the interventional trial papers (biomarker and harmful or potentially harmful constituent terms provided) were:

- 1-NA (1-aminonaphthalene)
- 1-OHP (1-hydroxypyrene)
- 2-NA (2-aminonaphthalene)
- 3-HPMA (3-hydroxypropylmercapturic acid): acrolein
- 3-OH-B[a]P (3-hydroxy(a)benzopyrene)
- 3-HMPMA (3-hydroxy-1-methylpropylmercapturic acid): crotonaldehyde
- 4-ABP (4-aminobiphenyl)
- AAMA (acrylamide mercapturic acid): acrylamide
- B[*a*]P (benzo[*a*]pyrene)
- CEMA (2-cyanoethylmercapturic acid): acrylonitrile
- GAMA (glycidamide mercapturic acid)
- HEMA (2-hydroxyethyl mercapturic acid): ethylene oxide
- Mutagens *Salmonella* mutagenicity (YG1024) with S9
- MHBMA (monohydroxybutenyl mercapturic acid): 1,3-butadiene
- NNAL (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol): NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
- o-tol (o-toluidine): o-toluidine
- S-PMA (S-phenylmercapturic acid): benzene
- Total NNAL (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol): 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
- Total NNN (total N-nitrosonornicotine): N-nitrosonornicotine
- Total 1-OHP (total 1-hydroxypyrene): pyrene
- Total 3-OH-B[a]P (3-hydroxy-benzo(a)pyrene): benzo(a)pyrene
- TMA (trans, trans-muconic acid)
- S-BMA (S-benzylmercapturic acid): toluene, and
- SCN: thiocyanate a biomarker of exposure for hydrogen cyanide.

All 12 papers in this section were from trials conducted by the industry. The trial undertaken by British American Tobacco was based in Japan (3 papers), and the nine papers from Philip Morris reported on trials conducted in Japan (3), Poland (2), South Korea (1), the UK (1), and the USA (1). The location of one trial was not reported.

Tricker *et al.* published four papers in 2012 from trials conducted in Japan, South Korea, and the UK[412-415]. The numbers of participants for which outcome data were available were 72, 102, 128, and

160 across the four trials, so all analyses were per protocol and therefore did not include trial dropouts. Subjects were randomised into one of three or parallel groups, where the following heat-not-burn products with or without menthol (indicated by 'M') and conventional tobacco cigarettes were evaluated in comparison with smoking abstinence:

- The electrically heated cigarette smoking system with and without menthol, specifically the EHCSS series-K cigarette, the EHCSS-K3 cigarette, the EHCSS-K6 cigarette, and the EHCSS-K6M cigarette
- The following tobacco cigarettes: Marlboro non-menthol cigarettes with 6 mg tar and 0.5 mg nicotine delivery (M6J), the M4J(M), the Marlboro non-menthol cigarette United Kingdom (M6UK), the Philip Morris One cigarette (PM1), the Lark1 (1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO), and the Lark1M; and
- Smoking abstinence.

The Marlboro non-menthol cigarettes (M6J and M6UK) were chosen to represent the Japanese and UK cigarette markets, and the Lark1 was chosen to represent the South Korean cigarette market. Biomarkers of exposure to between 9 and 12 selected harmful and potentially harmful constituents of tobacco, as well as urinary excretion of mutagenic material, were assessed. The findings across Tricker *et al.*'s[412] [413-415] (2012) industry-based trials were reasonably consistent. The authors concluded that the trials showed statistically significant mean reductions in biomarkers of selected harmful and potentially harmful constituents of tobacco smoke, and reductions in excretion of mutagenic material in urine, of smokers who smoked their own cigarettes when they switched to use the EHCSS series-K lighter and smoked any of the EHCSS series heat-not-burn products at the final day of the trial, compared to baseline. In smokers who switched to smoking conventional tobacco cigarettes representative of the low-tar cigarette market, smaller mean reductions were observed, most of which were statistically significant. The largest mean reductions occurred in smokers who switched to smoking abstinence. Changes in serum concentrations of Clara cell 16-kDa protein could not be meaningfully interpreted.

In an industry-based trial, Sakaguchi *et al.*[416] (2014) examined the impact of a prototype electrically heated cigarette in a population of 70 healthy Japanese male smokers. The trial authors concluded that exposure to most tobacco cigarette smoke constituents, except carbon monoxide, can be reduced by switching from the conventional cigarette (10 mg tar and 0.8 mg nicotine) to the prototype electrically heated cigarette. However, it should be noted that the test cigarette prototype was prepared by Japan Tobacco International for the study and was never commercially available.

Haziza *et al.*[417-419] published three industry-based trial papers between 2016 and 2020 reporting on the relationship between heat-not-burn products (with and without menthol), conventional tobacco cigarettes, and abstaining from smoking in trials conducted in Japan, Poland and the USA. In each trial, 160 subjects were assigned to one of three products (albeit with differences in the number of participants in each of the study arms), and a range of biomarkers of exposure to harmful and potentially harmful constituents in tobacco were assessed. In general, biomarker levels were reduced following use of heat-not-burn products compared with conventional cigarette use, and in some instances, biomarker levels were reported as approaching the levels observed in the smoking abstinence group.

Lüdicke *et al*. [420-422] published one trial paper in 2016, one in 2017 and one in 2018. The 2017 trial paper measured the impact of switching from smoking conventional tobacco cigarettes to the THS 2.1 on biomarkers of exposure to harmful and potentially harmful tobacco constituents in 42 people in a 5-day trial. In the 2018 paper, the authors reported on findings from 160 participants comparing the menthol THS 2.2, conventional tobacco cigarettes, and smoking abstention. In the 2016 paper, the authors reported on findings from 112 participants comparing carbon-heated tobacco products, conventional tobacco cigarettes, and smoking abstention. A similar array of biomarkers of exposure was examined in the studies. In the three papers, the authors reported decreasing levels of biomarkers following use of the THS 2.1, menthol THS 2.2 or carbon-heated tobacco product,

compared with conventional cigarette use and these approached the levels of biomarkers observed in the smoking abstinence group.

Gale *et al*.[423] of British American Tobacco conducted a randomised, controlled, parallel group open-label trial with clinical confinement and product exposure of 5 days' duration. Participants were randomised to one of six groups (non-menthol cigarette group, non-menthol glo™ THP 1.0 group, menthol cigarette group, menthol glo™ THP 1.0 group, iQOS THP group, and abstinence group) for 5 days of exposure, with approximately 30 participants in each group. More than 15 urinary biomarkers of toxicant exposure were assessed in this trial. Participants trialling the new-generation heat-not-burn cigarette, compared with participants using conventional cigarette products, showed fewer adverse effects on NOX2-derived peptide and 8-isoprostaglandin vitamin E. The heat-not-burn cigarette and the electronic vaping cigarette were associated with less damage than conventional tobacco cigarettes on flow-mediated dilation, hydrogen peroxide breakdown activity F2a-III, and on soluble CD40 ligand and soluble P-selectin. The heat-not-burn cigarette, and, to a lesser extent, the e-cigarette, exhibited a less evident impact on raising blood pressure than the conventional cigarette.

Table 58 Interventional trial papers on exposure to heat-not-burn toxins, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		Industry-based trials **Electrically heated cigarette smoking system**	
Tricker *et al.*[412] 2012a	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to nine selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke** (Marlboro cigarettes containing 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide (CO)) and levels of urinary excretion of mutagenic material in smokers and in users of one of two EHCSS series-K cigarettes, the EHCSS-K3 cigarette or the EHCSS-K6 cigarette. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–25 Marlboro non-menthol cigarettes per day for ≥4 weeks, with 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide per cigarette, at baseline) using: (1) Marlboro cigarettes (2) Electrically Heated Cigarette Smoking System EHCSS - K6 (0.3mg nicotine) (3) Electrically Heated Cigarette Smoking System EHCSS - K6 (0.3mg nicotine) (4) Philip Morris One cigarettes The authors concluded that the study showed strong mean reductions in uptake of selected harmful and potentially harmful constituents in cigarette smoke, and reductions in excretion of mutagenic material in urine, from baseline to day 8 in M6UK non-menthol cigarette smokers who switched to smoking either the EHCSS-K3 or the EHCSS-K6 non-menthol cigarettes. Smokers who switched to smoking PM1, a conventional combustible tobacco non-menthol cigarette representative of the low-tar cigarette market, showed smaller reductions. The largest mean reductions occurred in smokers who stopped smoking.	Randomised controlled trial
Tricker *et al.*[413]	Less harmful than conventional	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially**	Randomised controlledtrial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
2012b	combustible tobacco cigarettes	**harmful constituents in conventional combustible tobacco cigarette smoke** (Lark1 cigarettes containing 1.0 mg tar, 0.1 mg nicotine, and 1.5 mg carbon monoxide (CO)), and levels of urinary excretion of mutagenic material. The study involved the following three groups: smokers of Lark1 cigarettes; users of EHCSS-K3 cigarettes (3 mg tar, 0.2 mg nicotine, and 0.6 mg carbon monoxide (CO)); and non-smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–30 cigarettes with 1.0–3.0 mg tar daily and smoke 10-30 Lark1 for ≥ 2 weeks at baseline) using: (1) Lark One cigarettes (2) Electrically Heated Cigarette Smoking System EHCSS‐K3 (3) smoking abstinence The authors concluded that the study showed mean reductions in biomarkers of exposure to 10 of 12 selected harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke (1,3-butadiene, 2-naphthylamine, 4-aminobiphenyl, acrylamide, benzene, carbon monoxide (CO), nicotine, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), pyrene, and o-toluidine) from baseline to day 8 in Lark1 smokers who switched to smoking EHCSS-K3 cigarettes. No change was determined for biomarkers of exposure to crotonaldehyde and acrolein. In smokers who continued to smoke Lark1 cigarettes, exposure to the majority of the harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke (1,3-butadiene, 2-naphthylamine, 4-aminobiphenyl, acrylamide, benzene, carbon monoxide (CO), crotonaldehyde, nicotine, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and o-toluidine) increased, while biomarkers of exposure to acrolein and pyrene decreased. With the exception of 1,3-butadiene, 2-naphthylamine, benzene, carbon monoxide (CO), nicotine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), few of the changes reached the level of statistical significance. The largest mean reductions in all harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke occurred in smokers who switched to no smoking. Excretion of mutagenic material in urine was significantly decreased in the EHCSS-K3 and no-smoking groups, and was significantly increased in the Lark1 group.	
Tricker *et al.* [414] 2012c	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially harmful constituents of tobacco smoke** (in Marlboro cigarettes containing 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide (CO)), and on levels of urinary excretion of mutagenic material. The study involved the following four groups: users	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		of the EHCSS-K6 (5 mg tar, 0.3 mg nicotine, and 0.6 mg carbon monoxide (CO)); users of the EHCSS-K3 (3 mg tar, 0.2 mg nicotine, and 0.6 mg carbon monoxide (CO)); smokers who switched to smoking Lark1 cigarettes (1 mg tar, 0.1 mg nicotine, and 2.0 mg carbon monoxide (CO)); and non-smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–30 Marlboro non-menthol cigarettes per day for ≥2 weeks, with 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide per cigarette, at baseline) using: (1) Marlboro cigarettes (2) Electrically Heated Cigarette Smoking System (EHCSS - K6 0.3mg nicotine) (2) Electrically Heated Cigarette Smoking System (EHCSS - K6 0.2mg nicotine) (4) Lark One cigarettes The authors concluded that this study showed statistically significant mean reductions in biomarkers of exposure to selected harmful and potentially harmful constituents in tobacco cigarette smoke and in excretion of mutagenic material in urine of smokers who smoke the M6J cigarette and switched to using the EHCSS K lighter and smoking either the EHCSS-K3 or the EHCSS-K6 cigarette at day 8, compared to baseline. In smokers who switched to smoking the Lark1 cigarette, a conventional combustible tobacco cigarette representative of the low-tar cigarette market, smaller mean reductions were observed, most of which were statistically significant. The largest mean reductions occurred in smokers who switched to no smoking.	
Tricker *et al.*[415] 2012d	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke** (Marlboro Ultra Lights Menthol cigarettes, the M4J(M) (4 mg tar and 0.3 mg nicotine)), and on levels of urinary excretion of mutagenic material and serum Clara cell 16-kDa protein (CC16) in the following four groups: smokers of conventional combustible tobacco cigarettes; users of the M4J(M) cigarettes; participants who switched to smoking either the EHCSS-K6M cigarette (5 mg tar and 0.3 mg nicotine) or the Lark1 menthol cigarette (Lark1M) (1 mg tar and 0.1 mg nicotine); and non-smokers. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–30 menthol cigarettes per day for ≥2 months, with 3–6 mg tar, at baseline) using: (1) Marlboro Ultra Lights Menthol cigarettes (2) Electrically Heated Cigarette Smoking System menthol cigarette (EHCSS - K6(M)) (3) Lark One menthol cigarette (Lark1(M)) (4) smoking abstinence The authors concluded that this study showed reductions in the mean values of individual	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		biomarkers of exposure to selected harmful and potentially harmful constituents in tobacco cigarette smoke from baseline to day 5 or 6 in smokers of the M4J(M) cigarette who switched to using the EHCSS series-K lighter and smoking the EHCSS-K6M menthol cigarette. In smokers who switched to smoking the Lark1M menthol cigarette, a conventional combustible tobacco cigarette representative of the low-tar menthol cigarette market, reductions in exposure to individual harmful and potentially harmful constituents in tobacco cigarette smoke were smaller. The largest reductions in individual harmful and potentially harmful constituents in tobacco cigarette smoke occurred in smokers who switched to no smoking. Reductions in the mean excretion of mutagenic material in urine occurred in the EHCSS-K6M and no-smoking groups, but not in the M4J(M) and Lark1M groups. Changes in serum concentrations of Clara cell 16-kDa protein could not be meaningfully interpreted.	
		Prototype heated cigarette	
Sakaguchi *et al.* [416] 2014	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **changes in levels of biomarkers** of exposure in healthy smokers who switched to a prototype heated cigarette. Measures on 10 biomarkers of exposure (nicotine, carbon monoxide (CO), benzene, 1,3-butadiene, acrolein, hydrogen cyanide, crotonaldehyde, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), pyrene, and 4-aminobiphenyl), and urine mutagenicity, were recorded *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 20 cigarettes per day for ≥1 year, with 10–15 mg tar, and same brand for ≥ 8 weeks, at baseline) using: (1) prototype heated cigarette (2) 10 mg tar conventional cigarette The authors concluded that exposure to most tobacco cigarette smoke constituents, except carbon monoxide (CO), can be reduced by switching from a conventional combustible tobacco cigarette containing 10 mg tar to a prototype heated cigarette.	Semi-randomised controlled trial
		Tobacco heating system	
Haziza *et al.* [417] 2016a	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of harmful and potentially harmful constituents** in smokers continuing to smoke conventional combustible tobacco cigarettes, smokers switching to the THS 2.2, and smokers abstaining from smoking for 5 days. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 10 non-menthol cigarettes per day for ≥4 weeks, with a maximum yield of 1 mg nicotine per cigarette, and smoked ≥ 3 years, at baseline) using: (1) Tobacco Heating System 2.2 (THS 2.2)	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		(2) conventional combustible tobacco cigarettes (3) smoking abstinence The authors concluded that switching from smoking conventional combustible tobacco cigarettes to using the THS 2.2 resulted in substantial reductions in exposure to 15 selected harmful and potentially harmful constituents of tobacco smoke. The kinetics and the magnitude of the decrease in levels of biomarkers of exposure observed in the THS 2.2 group were approaching the levels observed in the smoking abstention group for the majority of the biomarkers of exposure. Nicotine uptake was similar between the THS 2.2 and conventional combustible tobacco cigarette groups at the end of the 5-day exposure period; after users had started to adapt to a new product, and with a transitional period of changing puffing behaviour, users were able to achieve their desired nicotine level. The combination of the results of nicotine exposure and subjective effect measures indicated that the THS 2.2 offered comparable satisfaction, with regard to taste and sensorial experience, to that which was observed in conventional combustible tobacco cigarette smokers. No adverse event or severe adverse events were reported during this study, with the total number of adverse events being very low and evenly balanced across study groups.	
Haziza *et al.*[418] 2016b	Less harmful than conventional combustible tobacco cigarettes	The authors reported on levels of **harmful and potentially harmful constituents** in smokers continuing to smoke conventional combustible tobacco cigarettes, smokers switching to the THS 2.2, and smokers abstaining from smoking for 5 days. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users with (smoke ≥ 10 non-menthol cigarettes per day for ≥4 weeks, with a maximum yield of 1 mg nicotine per cigarette, and smoked ≥ 3 years, at baseline) using: (1) ad libitum use of THS 2.2 (2) conventional combustible tobacco cigarette use (3) smoking abstinence, The authors concluded that biomarkers of exposure, except those associated with nicotine exposure, were significantly reduced in the THS 2.2 group compared with the conventional combustible tobacco cigarette group, and approached the levels observed in the smoking abstinence group. Increased product consumption and total puff volume were reported in the THS 2.2 group. However, exposure to nicotine was similar to that in the conventional combustible tobacco cigarette group at the end of the confinement period. Reduction in the urge to smoke was comparable between the THS 2.2 and conventional combustible tobacco cigarette groups, and the THS 2.2 product was well tolerated.	Randomised controlled trial
Haziza *et al.*[419]	Less harmful than conventional	The authors reported on **levels of biomarkers of exposure** in smokers continuing to smoke	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
2020	combustible tobacco cigarettes	conventional combustible tobacco cigarettes, smokers switching to the menthol THS 2.2, and smokers abstaining from smoking for 5 days in a confined setting, followed by an 86-day ambulatory period. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 10 non-menthol cigarettes per day for 4 weeks, with a maximum yield of 1 mg nicotine per cigarette, and smoked ≥ 3 years, and did not plan to quit, at baseline) with: (1) menthol Tobacco Heating System (mTHS) 2.2 (2) menthol cigarettes (3) smoking abstinence The authors concluded that switching to the menthol THS 2.2 led to significant reductions in exposure to Total NNAL the molar sum of 4-(methylnitrosamino)-1-(3-pyridy1)-1-butanol and its O-glucuronide conjugate, Total NNN the molar sum of free and conjugated NNN i.e.N-nitrosonornicotine, carboxyhemoglobin, monohydroxybutenyl mercapturic acid, 3-hydroxypropylmercapturic acid, S-phenylmercapturic acid1-hydroxypyrene, 4-aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, o-toluidine, Cyanoethylmercapturic Acid, Hydroxybutyl Mercapturic Acid, HMPMA, and benzo[a]pyren after 5 days in confinement, which were maintained throughout the subsequent ambulatory period of 86 days. The reductions were comparable to those observed upon smoking abstinence.	
Lüdicke *et al.* [421] 2017	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the impact of switching to the THS 2.1 on biomarkers of **exposure to harmful and potentially harmful constituents.** *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 10 non-menthol cigarettes per day for 4 weeks, with a maximum yield of 1 mg nicotine per cigarette, and smoked ≥ 3 years, at baseline) using: (1) conventional combustible tobacco cigarette (2) Tobacco Heating System THS 2.1 The authors concluded that the THS 2.1 is a promising alternative to smoking conventional combustible tobacco cigarettes. Notwithstanding possible use adaption through consumption or puffing behaviour, the exposure to harmful smoke constituents was markedly reduced following use of the new heat-not-burn tobacco product platform.	Randomised controlled trial
Lüdicke *et al.* [422] 2018b	Less harmful than conventional combustible tobacco cigarettes	The authors reported on the impact of switching to the menthol THS 2.2 on **biomarkers of exposure to harmful and potentially harmful constituents** relative to smoking menthol conventional combustible tobacco cigarettes and smoking abstinence. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke ≥ 10 menthol cigarettes per day for	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		4 weeks, with a maximum yield of 1 mg nicotine per cigarette, and smoked ≥ 3 years, at baseline) using: (1) menthol Tobacco Heating System 2.2 (mTHS) (2) conventional combustible tobacco cigarettes The authors concluded that switching from menthol conventional combustible tobacco cigarettes to the menthol THS 2.2 significantly reduced exposure to harmful and potentially harmful constituents relative to continuing smoking menthol conventional combustible tobacco cigarettes, with concentrations in those who switched being similar to the concentrations observed following smoking abstinence in Japanese adult smokers.	
		Carbon-heated tobacco product	
Lüdicke *et al.* [420] 2016	Less harmful than conventional combustible tobacco cigarettes	The authors aimed to investigate the effects of exposure to selected **harmful and potentially harmful constituents** of conventional combustible tobacco cigarette smoke in adult smokers who switched to a carbon-heated tobacco product, compared with adult smokers who continued to smoke conventional combustible tobacco cigarettes and those who abstained from smoking for 5 days. *Comparative groups* Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–30 cigarettes per day for 4 weeks, with a maximum tar yield of 10 mg per cigarette, and smoked ≥ 5 years, at baseline) using: (1) conventional combustible tobacco cigarette smoking ad libitum (2) carbon-heated tobacco product (CHTP) version MD2-E7 ad libitum The authors concluded that the results provide clear evidence supporting a reduction in the level of exposure to harmful and potentially harmful constituents of tobacco cigarette smoke in smokers who switched to a carbon-heated tobacco product under controlled conditions, and that the reduction was similar to that observed in the smoking abstinence group.	Randomised controlled trial
		glo™ THP 1.0 versus IQOS/THS	
Gale *et al.* [423] 2018	Both heat-not-burn products equal	The authors reported on the relationship of using two tobacco heating products (the glo™ THP 1.0 or the in-market comparator, the IQOS/THS) with **biomarkers of toxicant exposure.** Comparative groups Comparison(s) of conventional combustible tobacco cigarette users (smoke 10–30 menthol cigarettes per day for ≥ 3 years, at baseline) using: (1) a 7-mg/cig ISO tar combustible tobacco non-menthol cigarette (2) glo™/THP1.0 with non-menthol Neostiks (3) a 7-mg/cig ISO tar combustible tobacco menthol Cigarette (4) glo™/THP1.0 with menthol Neostiks Note: The iQOS/THS product with non-menthol tobacco consumables was also studied as an in-market comparator product. Only those smokers who regularly smoke	Randomised controlled trial

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins	Trial design
		mentholated cigarettes were randomized to use mentholated products during the study The authors concluded that switching from smoking to using THPs resulted in significant reductions in biomarkers of exposure for selected smoke constituents. For most of these biomarkers, the speed and magnitude of the reductions were comparable to those observed during smoking cessation. In this clinical study, the use of the study THPs was safe and well tolerated with a small number of AEs reported that were not attributed to study product use. Together with pre-clinical data on glo™/THP1.0 showing reduced emissions and toxicological endpoints relative to cigarettes, glo™ has the potential to be a reduced exposure and/or reduced risk tobacco product when used by smokers whose cigarette consumption is displaced completely.	

5.4.2.9 Other outcomes: interventional trials

There were no interventional trials on the relationship between heat-not-burn products and other outcomes.

6 Discussion

6.1 Summary of findings

This mapping exercise describes findings from published peer-reviewed journal articles and organises the information in a way that enables discussion and decision-making by researchers, policy makers, and practitioners. This mapping exercise allows examination of the relationship between two nicotine-related products and their impact on health. Specifically, it addresses two questions posed by the Irish Department of Health. The first 'What are the public health benefits and harms of e-cigarettes?' and the second 'What are the public health benefits and harms of heat-not-burn tobacco products?' The HRB identified 388 papers eligible for inclusion in the report, 361 reporting the harms and benefits of e-cigarettes, and 28 reporting the harms and benefits of heat-not-burn tobacco products, with one paper reporting both exposures. The outcomes measured were clinically diagnosed diseases or injuries, biological risk markers for disease, measures of organ function, presence of toxins and toxicants, and self-reported signs and symptoms. These biological risk markers were: measures within the normally accepted clinical range indicative of health and well-being, and measures outside the normally accepted clinical range which are regarded as indicative of current or later disease (Tables 60 and 64).

6.1.1 E-cigarette summary map

6.1.1.1 Study design by United States National Academies of Sciences, Engineering, and Medicine (Academies of Sciences) umbrella terms: e-cigarettes

The 361 included studies on possible harms and benefits of e-cigarettes were mapped by study design and by the adapted Academies of Sciences' umbrella terms.[6] The number of study papers in each group is presented in Table 59. All types of epidemiological study designs are used to investigate the recent e-cigarette phenomenon. The highest number of studies are case reports, followed by interventional trials and cross-sectional surveys. Papers reporting surveillance data are also presented as they characterise clinical presentation of the harms and benefits of e-cigarettes at a community-level. Most of the observational and interventional studies identify associations between e-cigarettes and the outcomes of interest, but these associations do not prove causality. A well-conducted RCT adequately controls for confounding and the observed direction of effect may indicate a causal beneficial or harmful effect where the other essential criteria for causality are met. However, care must be taken in the area of e-cigarettes when generalising findings from the studied populations to other populations with different characteristics, and when generalising findings from populations where different kinds of interventions were used. In addition, the included studies have short follow-up periods and small sample sizes. Overall, it is difficult to generalise any e-cigarette trial findings to the general population. A total of 9% of the interventional trials were completed by the e-cigarette industry. The highest and second-highest number of studies by scientific heading and study design are shown in navy blue, and light blue shading, respectively, in Table 59. The majority of studies were completed on the acute effects of e-cigarettes, specifically on acute respiratory conditions and on injuries and poisonings. Relatively little research was published on e-cigarettes and cancers, on e-cigarettes and developmental and reproductive effects, or on e-cigarettes and the effects of passive nicotine uptake by involuntary exposure.

Table 59 Study papers on e-cigarettes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Total	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Total	**361**	**94**	**37**	**34**	**86**	**2**	**22**	**86**
Dependence and abuse liability	**60**	0	2	1	21*	0	10	26*
Cardiovascular diseases	**32**	2	1	0	5	0	3	21
Cancers	**7**	0	1	0	5	1	0	0
Respiratory diseases	**78**	23	8	4	21	1	5	16
Oral diseases	**24**	4	0	0	14	0	3	3
Developmental and reproductive effects	**2**	0	0	1	0	0	1	0
Injuries and poisonings	**100**	49	24	27	0	0	0	0
Exposure to e-cigarette toxins	**28**	4	1	1	9	0	0	13
Other outcomes	**30**	12	0	0	11	0	0	7

*The highest and second-highest number of studies by scientific heading and study design are shown in navy blue, and light blue shading, respectively.

6.1.1.2 Study characteristics: e-cigarettes

The peer-reviewed published studies were drawn from all over the globe, with the highest number from the USA, followed by Italy. The study participants were mainly adults. However, young children were common in studies examining injuries and poisonings. Never-smokers were also observed to use e-cigarettes.

The outcomes measured were clinically diagnosed diseases or injuries, biological risk markers for disease, measures of organ function, toxins and toxicants, and self-reported signs and symptoms. The follow-up periods in the mapped studies ranged from minutes to 24 months and did not have a sufficient timeframe to detect chronic disease outcomes such as cardiovascular diseases, cancers, or chronic respiratory diseases. A total of 8 (9%) of the 86 interventional trials reported on an exposure outcome effect measured between 12 weeks and 24 months, while the remaining 78 trials reported on outcomes measured within 8 weeks or less. The study designs were a mix of randomised controlled trials, randomised and non-randomised crossover trials including Latin square trials, and non-randomised before and after studies.

It is important to note that e-cigarettes and their e-liquids were not a standard intervention in the included studies; rather, they are an umbrella term for a device that delivers nicotine and other products including flavourings. By 2017, more than 611 e-cigarette brands were available, and to generalise findings from the randomised trial of one specific e-cigarette as an assessment of the expected impact of all e-cigarette types discounts the differences in the chemical composition of various e-cigarette brands and types. The content of the e-liquids was another confounding factor due to the variation in nicotine dosages and other contents. To date, of the 86 trials examining health benefits and harms in people included in the map, only 62 trials identified the device used and only 39 e-cigarette devices were tested out of 611 ever available on the market or 433 believed to be currently available, which gives a sense of the small number of e-cigarette devices that have been tested in trials involving people, and the small number of corresponding research papers published in peer-reviewed literature.

The variations in e-cigarettes tested included: disposable e-cigarettes which were not refillable, e-cigarettes which used replaceable prefilled cartridges, and tank models which were filled with liquids by the user. Disposable e-cigarettes consisted of batteries with primary (not chargeable) cells, whereas e-cigarettes with rechargeable cells used replaceable prefilled cartridges or had refillable tanks.

The content of the e-liquids was another confounding factor. The variation in nicotine dosages is noteworthy, specifically in trials seeking to assess issues around dependence and abuse liability. This is particularly relevant given that the higher nicotine levels, specifically reported as between 18 and 36 mg/mL, have been demonstrated to be the only doses resulting in a reliable increase in nicotine plasma concentrations. Reports on the carrier solution, a mixture of propylene glycol and vegetable glycerine, varied from 40.0% to 72.5% for propylene glycol and from 18.8% to 40.8% for vegetable glycerine. A range of other products was found in the carrier solution, for example, the presence of metals (cadmium, lead, mercury, and chromium), volatile organic compounds (pyrazine and 2,3-dimethylpyrazine), and other products associated with nicotine (myosmine).

Table 60 Study characterisation

Characteristic	Descriptor
Study design	Case report, case series, information or surveillance system report, cross-sectional survey, case-control study, longitudinal cohort study, and interventional trials to test interventions (which included randomised controlled, randomised and non-randomised crossover, non-randomised before and after, or Latin square)
Age	All age groups, but a high proportion of young adults Young children were associated with poisonings
Sex	Both sexes, but more males than females
Continent or country	Africa (Egypt, South Africa), Americas (Canada, the USA), Asia (Hong Kong, China, Indonesia, Japan, Malaysia, South Korea, Saudi Arabia, Turkey), Australia, and Europe (Belgium, Denmark, France, Greece, Germany, Hungary, Italy, Poland, Romania, Russia, Spain, Sweden, and the UK)). There were two worldwide surveys and two cross-European studies.
Population size	Wide variation in study numbers, ranging from 1 to 486,303
Study duration	Minutes to 24 months. Varied by study design. Case report, case series, and information or surveillance system report consisted of one event per case where the exposure was followed in a short period of time by the outcome Case-control studies looking back from disease to exposure Cross-sectional survey through a single point in time interview Cohort studies with at least one follow-up. The longest follow-up period was 24 months. Interventional trials vary in follow-up time, ranging from minutes to days, weeks, or months, and up to 24 months.
Intervention or exposure	E-cigarettes are not standard interventions. E-cigarette users were grouped as never, former, occasional, and daily users. Each of the four groups was further subdivided according to e-cigarette use (such as nicotine and non-nicotine) and dual use.
Outcomes	The dependence and abuse liability outcomes assessed were: patterns of e-cigarette use, cravings, desire to smoke, dependence, sleeping patterns, appetite control, cognitive performance or memory, depression, suicidality, and blood or brain nicotine levels. The measures assessed in order to evaluate cardiovascular health included: blood pressure, blood counts, heart rate, body weight, myocardial function, arterial stiffness and arterial pressure, endothelial progenitor cells, vagal and sympathetic nerve activity, antioxidant parameters, microvascular endothelial function and oxidative stress, and vascular and haemodynamic measures. Carcinogenic risk was assessed through a variety of measures, including the total nicotine equivalents or dose; the nicotine metabolite ratio; tobacco-specific smoking-related carcinogens for oral, oesophageal, lung, and bladder cancers; and cytologic examination of micronuclei in the oral mucosa. The measures used to assess respiratory diseases were: signs and symptoms of possible respiratory diseases, respiratory function tests, measures of tissue damage or stress, measures of toxicity in body tissue and exhaled breath, and the propensity for respiratory diseases. The measures of oral diseases were: full-mouth plaque index, bleeding on probing, clinical attachment loss, probing depth, gum disease, bone loss around teeth, gingival inflammation, perfusion of buccal mucosal tissue, infection markers, tumour markers, and parent drug and metabolites in oral fluid. The developmental and reproductive effects measured were: prevalence of e-cigarette use during pregnancy and the lactating period, and the effects of e-cigarettes on weight for gestational age at birth. Injuries and poisonings were measured using chemical laboratory analysis and were classified using existing international classification rules.

Characteristic	Descriptor
	The toxins and toxicants measured were urinary nicotine metabolites, minor tobacco alkaloids, arsenic and arsenic compounds, tobacco-specific nitrosamines, metals, polycyclic aromatic hydrocarbons, volatile organic compounds, and toxic gases.

6.1.1.3 Absolute health-related harms associated with e-cigarettes

Most observed clinical harms were due to acute events associated with the use of e-cigarettes and were reported in descriptive case studies, surveillance system papers, and cross-sectional survey papers (Table 61).

The acute effects included poisonings (mainly nicotine and some e-liquid constituents), injuries (mainly burns and some fractures), and respiratory diseases (mainly injuries to the lungs and exacerbation of asthma). There were fatalities among the poisonings and respiratory disease cases, and long-term disability among some burn cases. Twelve papers reported on the outbreak of lung injury associated with e-cigarettes or vaping between June and October 2019 across a range of American states. These papers presented acute effects of e-cigarette use that in some cases resulted in fatalities. Both the poisoning cases and the respiratory disease cases highlighted a possible association between e-cigarettes and the use of other drugs such as alcohol, synthetic cannabinoids, and opiates. The categories 'injuries and poisonings' and 'exposure to e-cigarette toxins' were closely linked. Poisonings resulted in acute adverse events, while exposure to toxins covered the detection of the slow build-up of toxins and toxicants (such as metals and volatile organic compounds) in the body, which are biomarkers for future disease and can cause tissue damage or cancer. In addition, hand and mouth contact with e-cigarettes was associated with harms such as dermatitis (five cases) and reduced blood circulation (and delayed wound healing in three case reports).

Seven studies identified an association between e-cigarettes and depression, and three studies identified an association with suicidality. Two trials reported that e-cigarettes have potential for abuse liability and another two trials reported that e-cigarettes created dependence and abuse liability among never smokers.

There was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds. Four cross-sectional surveys on cancers identified the presence of carcinogens for lung, oral, and oesophageal cancer, and one identified biomarkers for bladder cancers. In addition, two case report papers described two e-cigarette users with oral cancer that could not be attributed to another exposure or factor. With respect to dental and periodontal health, seven papers found that e-cigarette users are prone to developing plaque, caries, or periodontal disease. Three cross-sectional survey papers identified markers for oral infection in e-cigarette users. One surveillance system paper reported on cases of e-cigarette vaping during pregnancy, and there was evidence from one longitudinal study that e-cigarettes may be associated with newborns being small for gestational age. A second paper based on prospective longitudinal study design and published after the mapping search period did not uphold the first longitudinal study findings.[288] Five studies identified that passive nicotine intake had occurred in the participants involved in these studies, and the authors of these studies reported that negative effects of passive nicotine intake will require further investigation.

Table 61 Possible e-cigarette-related negative outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Harms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Unsuccessful cessation attempt			1	1 Associated with smoking initiation in adolescents			2
	Dependence				1		2	5
	Higher dependence on e-cigarettes than on conventional tobacco cigarettes				2			
	Depression				5		4	
	Suicidality				4			
	Sleep disturbance				3			
	Weight control				2			
	Dual use						●	1
	Higher nicotine uptake than in smokers of conventional tobacco cigarettes							1
Cardiovascular diseases	Atrial fibrillation	1		·		·		
	Coronary artery dissection	1						
	High levels of cardiotoxic volatile organic compounds		1 Indicator of tissue damage					
	Acute cardiovascular conditions				3		1	
	Increased heart rate							3
	Increased blood pressure							4
	Platelet activity or clotting							1
	Arterial stiffness		Indicator of tissue damage					2

Study design by adapted Academies of Sciences' umbrella terms	Harms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
	Oxidative stress		Indicator of tissue damage					3
	Reduced local circulation							2
Cancers	Oral carcinoma		1					
	Presence of carcinogens for lung, oral, and oesophageal cancers				2			
	Bladder cancer biomarkers					1		
	Presence of carcinogens in e-cigarette toxin papers							1
Respiratory diseases	Lung injury	7	5	4	1	1 Tetrahydrocannabinol		1
	Bronchiolitis or pneumonia	6	1					
	Other respiratory disease or symptoms	7	1		5		1	1
	Asthma (active or passive vaping)		1		8			1
	Sputum abnormalities				1			
	Genes displaying decreased expression				1			
	Higher rates of chronic respiratory disease than in non-users						1	
	Equal rates of chronic respiratory disease in smokers, e-cigarette vapers, and dual users of e-cigarettes and conventional						1	

Indicator of tissue damage

Study design by adapted Academies of Sciences' umbrella terms	Harms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
	tobacco cigarettes							
	Reduced vascular function to the lungs							4
	Reduced physiological function							8
Oral diseases	Abnormalities of mucosal membranes or the tongue	3						
	Dental caries	1			4			
	Periodontal disease				4			
	Higher level of periodontal disease compared to non-users						1	
	Increase in gingival inflammation when tobacco smokers switched from smoking to vaping				1			1
	Markers for oral infection				2			
Developmental and reproductive effects	Vaping in pregnancy			1				
	Newborns small for gestational age						1	
Injuries	Blast injuries	8	13	3				
	Burns	10	6	1				
	Fractures	4						
	Combination burns and fractures	6						
Poisonings	Nicotine/e-liquid	19	4	23				

Study design by adapted Academies of Sciences' umbrella terms	Harms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
	Opiate	1	1					
	Synthetic cannabinoids	1						
Exposure to e-cigarette toxins	Dermatitis	3						
	Neurological and cardiac disturbances	1						
	Second- or third-hand nicotine intake			1				1
	Metals		Indicator of tissue damage		3			
	Volatile organic compounds		Indicator of tissue damage		2			3
	Other toxins				1			1

6.1.1.4 Relative health-related harms associated with e-cigarettes

Due to the mapping nature of the work undertaken here, we have stated the direction of effect for the observed relationships in observational and interventional studies, but not quantified the direction of effect. It is important to consider if harms or benefits from e-cigarettes or heat-not-burn tobacco products are greater or less than harms or benefits arising from the use of conventional tobacco cigarettes or other nicotine products which is defined as a relative effect.

As this is an evolving research area, it is too early to identify definitive chronic disease outcomes comparable to disease outcomes attributable to conventional cigarette use. There was variation in the direction of the impact of e-cigarettes on respiratory, cardiovascular, and oral disease outcomes, sometimes of a discordant nature. Some respiratory, cardiovascular, and oral diseases were noted to be less harmful in e-cigarette users than in conventional cigarette smokers but were as harmful in dual users (i.e. users of both conventional tobacco cigarettes and e-cigarettes) (Table 62). For example, with respect to respiratory diseases, one trial reported steady, progressive improvements in certain exhaled breath measurements and symptom scores following the switch from conventional tobacco cigarettes to e-cigarettes. Five trials reported that e-cigarettes were less harmful to lung function than conventional tobacco cigarettes. However, nine trials suggested that e-cigarettes damage the respiratory system by reducing vascular function to the lungs and/or reducing physiological function. Some examples of the findings for cardiovascular diseases are: four trials examined the effects of e-cigarettes on arterial stiffness, one trial reported no effect on arterial stiffness and three trials reported an increase in arterial stiffness. Four trials plus a fifth post-review non-randomised prospective study examined a combination of oxidative stress and vascular function; one trial reported a benefit was identified and one trial reported no harm was identified while three trials reported increased oxidative stress related to e-cigarettes. Six trials reported on the relationship between e-cigarettes and heart rate and/or blood pressure; two trials reported no effect and four trials reported a harmful effect. With respect to oral diseases, one trial concluded that e-cigarettes may improve blood flow to the oral mucosa while another trial concluded that there was a

statistically significant increase in gingival inflammation when tobacco smokers switched from smoking to vaping for 2 weeks.

Some biomarkers for lung, oral, and oesophageal cancers were noted to be lower in e-cigarette users than in conventional cigarette smokers. For example, four cross-sectional surveys examined the toxicity of conventional tobacco cigarettes and e-cigarettes when taken together or alone. These surveys showed that conventional cigarette smokers and dual users of conventional tobacco cigarettes and e-cigarettes had similar levels of urinary toxicants and carcinogen metabolites, whereas exclusive e-cigarette users had lower levels and non-users had the lowest levels. In addition, nine trial papers reported that toxin levels associated with smoking conventional tobacco cigarettes were lower in persons who had switched from using conventional tobacco cigarettes to using e-cigarettes. Smokeless tobacco product users and e-cigarette users had polycyclic aromatic hydrocarbon biomarkers somewhere between the levels found in conventional cigarette smokers and in non-smokers.

One study found that participants who were users of both e-cigarettes and conventional tobacco cigarettes had a lower level of dependence on e-cigarettes than on conventional tobacco cigarettes; however, this finding was not consistent across other studies. One trial found that use of e-cigarettes decreased cigarette consumption by 50% without causing significant nicotine withdrawal symptoms or increasing negative mental health symptoms in patients with chronic schizophrenia who smoked and did not intend to quit. Eight trials reported that using e-cigarettes reduced craving-like sensations in conventional cigarette smokers, whereas five trials reported that e-cigarettes did not reduce craving-like sensations. Two trials reported lower nicotine uptake in e-cigarette vapers than in conventional cigarette smokers, but another three trials reported similar nicotine uptake in vapers when compared to smokers.

Table 61 Possible e-cigarette-related harms, but less harmful than those related to conventional tobacco cigarettes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Harm reduction when compared to conventional tobacco cigarettes	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Reduced abuse liability				1			2
	Only modest weight increases with uptake of e-cigarettes						1	
	Lower nicotine uptake in vapers than in smokers							1
Cardiovascular diseases	Reduced cardiac ischaemia				1			
	Reduced heart rate							1
	Reduced blood pressure						1	1
	Less arterial stiffness							1

Study design by adapted Academies of Sciences' umbrella terms	Harm reduction when compared to conventional tobacco cigarettes	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Cancers	Lower levels of tobacco-related carcinogens				3			
Respiratory diseases	Effects on voice were mild				1			
	Reduction of respiratory symptoms				1			1
	Reduction of asthma and chronic obstructive pulmonary disease symptoms				1		3	
	Lower negative effect on lung function							4
Oral diseases	Less dental and periodontal health harm compared to conventional tobacco cigarettes				2		2	
Developmental and reproductive effects				No harm reduction identified				
Injuries				No harm reduction identified				
Poisonings				No harm reduction identified				
Exposure to e-cigarette toxins	Potentially harmful tobacco constituents				4			8

6.1.1.5 Health-related benefits associated with e-cigarettes

The evidence map featured few benefits of e-cigarettes reported in the examined studies (Table 63). The most common relative benefits, reported by a small number of heavy smokers of conventional tobacco cigarettes, were smoking cessation and smoking reduction. A state of stable dependence was categorised as a benefit in one paper. In a few studies, e-cigarette vaping was used as a way to minimise weight gain post-cessation of conventional cigarette smoking. One study claimed that e-cigarettes may better facilitate control of blood pressure (compared with smoking cigarettes), but all of these study participants were also prescribed personally titrated antihypertensive regimes. E-cigarettes may improve blood flow to the oral mucosa postoperatively in the non-smoker population, but only one small trial paper reported better blood circulation while three case studies reported reduced blood circulation and delayed wound healing. Four case report participants reported improvement in chronic disease symptoms and associated the improvement with the initiation of e-cigarette use (reduction of ulcerative colitis symptoms in one case, reversal of a blood condition in one case, recovery from chronic tonsillitis in one case, resolution of chronic nasal infection in one case, and reduction of Parkinson's disease symptoms in one case).

6.1.1.6 Summary statement on e-cigarette health-related harms, harm reduction, and benefits

The e-cigarette-related health harms, harm reduction, and benefits known to date are presented in this mapping exercise. However, there may be unknown harms. Most of the observed clinical harms were due to acute harmful events associated with the use of e-cigarettes and were reported in descriptive case studies, surveillance system papers, and cross-sectional survey papers.

The acute harms included poisonings (mainly nicotine and some e-liquid constituents), injuries (mainly burns and some fractures), and respiratory diseases (mainly injuries to the lungs and exacerbation of asthma). There were fatalities among the poisonings and respiratory disease cases, and long-term disability among some burn cases. Both the poisoning cases and the respiratory disease cases highlighted a possible association between e-cigarettes and the use of other drugs such as alcohol, synthetic cannabinoids, and opiates. There was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds. Four cross-sectional surveys on cancers identified the presence of carcinogens for lung, oral, and oesophageal cancer, and one identified biomarkers for bladder cancers. Some respiratory, cardiovascular, and oral diseases were noted to be less harmful in e-cigarette users than in conventional cigarette smokers, but were as harmful in dual users (i.e. users of both conventional tobacco cigarettes and e-cigarettes). However, these respiratory, cardiovascular, and oral disease findings were not consistent across all studies. The evidence map featured few reported benefits. The most common benefits, which were reported by a small number of heavy smokers of conventional tobacco cigarettes, were smoking cessation and smoking reduction.

Alongside this map, two systematic reviews [424] [425] on e-cigarettes were completed by the HRB. In the first review, we found that e-cigarettes were not more effective than approved nicotine replacement therapies (NRTs), which questions the need for e-cigarettes as a smoking cessation intervention. In the second review, we found that e-cigarettes were associated with initiation of conventional cigarette smoking among adolescents, which identifies a potentially serious harm. In addition, we note that many studies showed that dual use (of both e-cigarettes and conventional tobacco cigarettes) was not less harmful than smoking conventional tobacco cigarettes alone, thereby raising questions about the smoking reduction benefit of e-cigarettes. However, long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of heat-not-burn tobacco products and e-cigarettes, have a positive or negative impact on later life health outcomes. Generally, our thematic findings align with the high-level findings of six reviews and has some contrasting findings with one systematic review. Given the time gap between the existing systematic reviews and our mapping exercise, we identified additional recent papers covering oral diseases as well as developmental and reproductive effects associated with e-cigarettes.

Table 62 Possible e-cigarette-related beneficial outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Benefit	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	Smoking cessation		2 Not more effective than NRTs		1		3	
	Reduction						1	3
	Satisfaction				1			
	State of stable dependence						1	1
	Reduced cravings or withdrawal symptoms							2
	No or limited weight gain						1	1
Cardiovascular diseases		No benefits identified						
Cancers		No benefits identified						
Respiratory diseases	Resolution of chronic tonsillitis	1						
	Resolution of chronic nasal infection	1						
	Reverse lung damage and respiratory symptoms							2
Oral diseases	May improve blood flow to the oral mucosa							1
Developmental and reproductive effects		No benefits identified						
Injuries		No benefits identified						
Poisonings		No benefits identified						

Study design by adapted Academies of Sciences' umbrella terms	Benefit	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Exposure to e-cigarette toxins								1

6.1.2 Heat-not-burn tobacco products summary map

6.1.2.1 Study design by adapted Academies of Sciences' umbrella terms: heat-not-burn tobacco products

The 28 included published, peer-reviewed studies on possible harms and benefits of heat-not-burn tobacco products have been mapped by study design and by the adapted Academies of Sciences' umbrella terms (Table 64).[6] There were two case reports and one cross-sectional survey covering these products. There were 25 interventional trials, 23 of which were completed by authors working in the tobacco industry and 2 of which were completed by authors in universities, indicating a dearth of independent research on heat-not-burn tobacco products. Among the 25 published interventional trial papers, just under one-half (12) reported biomarkers of exposure to harmful or potentially harmful smoke constituents (see listing on Appendix 8). Eight interventional trial papers reported outcomes of cardiovascular health, and this represented the second most reported area of interest. One crossover interventional trial paper reported on measures of respiratory function, and four interventional trial papers reported on measures of dependence and abuse liability. The mapped interventional trials' follow-up periods ranged from minutes to 24 weeks and were not long enough to detect heat-not-burn chronic disease outcomes such as cardiovascular diseases, cancers, or chronic respiratory diseases. No peer-reviewed studies on humans were published on cancers, oral diseases, or developmental and reproductive effects up to mid-November 2019. There were no acute poisonings or injuries as a result of heat-not-burn tobacco products, but the subject of toxicity is addressed under the adapted Academies of Sciences' umbrella term 'exposure to heat-not-burn toxins'.

Table 63 Study papers on heat-not-burn tobacco products, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Total	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Total	**28**	**2**	**0**	**0**	**1**	**0**	**0**	**25**
Dependence and abuse liability	**5**	0	0	0	1*	0	0	4*
Cardiovascular diseases	**8**	0	0	0	0	0	0	8
Cancers	**0**	0	0	0	0	0	0	0
Respiratory diseases	**3**	2	0	0	0	0	0	1
Oral diseases	**0**	0	0	0	0	0	0	0
Developmental and reproductive effects	**0**	0	0	0	0	0	0	0
Injuries and poisonings	**0**	0	0	0	0	0	0	0
Exposure to heat-not-burn toxins	**12**	0	0	0	0	0	0	12
Other outcomes	**0**	0	0	0	0	0	0	0

*The highest and second-highest number of studies by scientific heading and study design are shown in navy blue, and light blue shading, respectively.

6.1.2.2 Study characteristics: heat-not-burn tobacco products

In general, study participants were adults. However, there were some exceptions: adolescents were the subject of one cross-sectional study, and a 16-year-old male was the subject of one case report. Approximately one-half of the studies were conducted in Belgium, Italy, Poland, South Africa, the UK, and the USA, and approximately the same number were conducted in Asia (Japan and South Korea) (Table 65). The two case reports each described one individual's history of acute eosinophilic pneumonia; the cross-sectional survey reported findings from 60,040 participants, and the sample sizes in the remaining papers (all interventional trials) varied from 18 to 316 participants.

The majority of trials were classified as randomised controlled trials, or crossover trials; such designs, when well-designed and implemented, control for confounding. The time frames of 24 of the 25 interventional trials were short; outcomes were gathered within a 10-day period or less. For the remaining trial, outcomes were gathered for 24 weeks. Biological measures were frequently gathered minutes or hours after exposure. The data collection time frames were adequate to report on transient effects following short-term heat-not-burn tobacco product use, but not the possible deleterious effects arising from long-term exposure. In general, the impact of heat-not-burn tobacco product use on outcomes beyond the short trial time frame parameters was not quantified.

It is important to note that heat-not-burn tobacco products were not standardised interventions (i.e. products), but rather that 'heat-not-burn tobacco products' is an umbrella term for devices with similar but not identical yields of tar, nicotine, and other products, such as carbon monoxide. There was variation in the types of devices examined, the chemical yield of the devices, and the trial comparator products used. The tested heat-not-burn devices included a variety of market brands and

prototypes which are well described in Section 5.4.1.2. Data on tar, nicotine, glycerine, and glycerol content levels were reported; sticks of heat-not-burn tobacco products had values ranging from 3 to 5 mg tar, 0.3 to 1.21 mg nicotine, 3.94 to 5.4 mg glycerine, and 2 to 50 mg glycerol per stick. Products with and without menthol flavouring were tested. Data on the chemical yield of the comparator conventional cigarette were not always available, as in several trials, participants were asked to bring and smoke their own preferred brand of conventional tobacco cigarettes. The available comparator data indicated that conventional tobacco cigarettes' tar levels varied from 1 to 11 mg, nicotine levels varied from 0.1 to 0.8 mg, and a carbon monoxide yield varied from 1.5 mg to 11 mg. In addition, comparisons with e-cigarette devices (blu PRO, Fontem, Netherlands) and snus (Camel Snus) were also reported.

Individual outcomes under the umbrella terms of 'dependence and abuse liability', 'cardiovascular diseases', 'respiratory diseases', and 'exposure to heat-not-burn toxins' were reported. The possible harm and benefit outcomes measured under the 'dependence and abuse liability' heading included cigarette craving/urge to smoke, withdrawal symptoms, nicotine and its metabolites, and various measures of carbon monoxide. The outcomes measured under the 'cardiovascular diseases' heading included a wide range of biomarkers that indicate organ and tissue damage. The reported respiratory outcomes included measures of airway resistance, lung function, and lung volume. The outcomes measured under the 'exposure to heat-not-burn toxins' heading were an extensive array of harmful or potentially harmful constituents of conventional cigarette smoke.

Table 64 Study characterisation

Characteristic	Descriptor
Study design	Case report, cross-sectional survey, and interventional trials to test interventions (randomised and crossover)
Age	16–65 years
Sex	Both sexes, but more males than females
Continent or country	Belgium, Italy, Japan, Poland, South Africa, South Korea, the UK, and the USA. Two studies did not report the geographical location of the study.
Population size	Wide variation in study numbers, ranging from 1 to 60,040 (interventional trials ranged from 18 to 316)
Study duration	Days to 24 weeks. Cross-sectional survey consisting of one interview Case report consisting of one event per case where the exposure was followed in a short period of time by the outcome Interventional trials vary in follow-up time, ranging from minutes to days or weeks
Intervention or exposure	Heat-not-burn tobacco products are not standard interventions. A range of heat-not-burn devices were used by study participants. Various editions of electrically heated cigarette smoking systems (e.g. EHCSS series-K), tobacco heating systems (e.g. THS 2.1), and a carbon-heated tobacco product prototype were tested in the interventional trials.
Outcomes	Clinically diagnosed harms, a wide range of biological risk markers for disease, measures of body function, and self-reported signs and symptoms associated with heat-not-burn product use. The possible harm and benefit outcomes measured for heat-not-burn product users under the 'dependence and abuse liability' heading included cigarette craving/urge to smoke, withdrawal symptoms, nicotine and its metabolites, and various measures of carbon monoxide. The outcomes measured under the 'cardiovascular diseases' heading included antioxidant status and oxidative stress, platelet activity, blood functions, endothelial function and dysfunction, lipid risk markers, cardiac risk markers, heart rate variability, cardiovascular risk and function, and factors related to oxygen uptake. The reported outcomes under the 'respiratory diseases' heading included measures of airway resistance, lung function, and lung volume. The outcomes measured under the 'exposure to heat-not-burn toxins' heading were an extensive array of harmful or potentially harmful constituents of tobacco smoke.

6.1.2.3 Absolute and relative health-related harms associated with heat-not-burn tobacco products

Three epidemiological study designs were used to investigate the impact of heat-not-burn tobacco products. These were case reports, one cross-sectional study, and interventional trials. The two case report papers described clinical diagnoses of acute eosinophilic pneumonia in a hospital setting (Table 65). The cross-sectional survey paper reported an increased odds ratio of perceived stress among adolescent heat-not-burn product users relative to non-tobacco users from a national-level survey in South Korea. Both study designs report associations between heat-not-burn tobacco products and the measured outcomes, but these study designs are not sufficient to determine a causal relationship. Four of the 25 interventional trials reported on dependence and abuse liability outcomes, and on related data measures that were gathered over an intervention period of between 2 and 8 days. The authors of the four papers concluded that substantial reductions in exposure to smoke constituents; effective delivery of nicotine; achievement of similar pharmacokinetic profiles as those observed

following conventional cigarette smoking; and momentary reduction of acute cigarette craving and withdrawal symptoms were observed among persons using heat-not-burn tobacco products.

Eight interventional trial papers reported on cardiovascular disease outcomes. Aside from one trial which lasted 24 weeks, outcome measures for the remaining trials were gathered over a period of between 2 and 10 days. The authors of the seven cardiovascular trial papers concluded that, compared with smoking conventional tobacco cigarettes or vaping e-cigarettes, cardiovascular disease outcome measures were less detrimental in heat-not-burn product users. However, adverse levels for all indicators were greater in heat-not-burn product users compared with non-smokers or persons who abstained from smoking during the trial period.

One interventional trial paper focused on measures of respiratory disease outcomes. This crossover trial paper reported on measures of respiratory function and found that using heat-not-burn products was less harmful to mid- to small-size pulmonary airways than smoking conventional tobacco cigarettes, but that it was more harmful than smoking abstinence.

The remaining 12 interventional trial papers examined in the heat-not-burn tobacco product section focused on a range of outcomes grouped within the 'exposure to heat-not-burn toxins' heading of the adapted Academies of Sciences' framework. In general, the reported direction of effect regarding the relationship between heat-not-burn tobacco products and measures of harmful or potentially harmful smoke constituents indicated lower levels of many of these constituents in heat-not-burn product users relative to smokers of conventional tobacco cigarettes, but the lowest levels of these constituents were observed among smoking abstainers. For example, in some papers, strong mean reductions in the uptake of selected harmful and potentially harmful constituents of cigarette smoke and in the excretion of mutagenic material in urine were noted. This change in levels from baseline to the timepoint of outcome measurement was observed in cigarette smokers who switched from smoking high-tar conventional tobacco cigarettes to smoking heat-not-burn tobacco products. Reductions were also reported in smokers who switched to smoking conventional tobacco cigarettes representative of the low-tar cigarette market; however, the magnitude of the reduction was lower. The largest mean reductions occurred in smokers who completely abstained from smoking, though this reducing effect was not true in all instances. For some studies, reports on the direction of effect were mixed. One interventional trial paper specifically reported no change in biomarker levels of exposure to crotonaldehyde and acrolein. One interventional trial paper reported that changes in serum concentrations of Clara cell 16-kDa protein could not be meaningfully interpreted in participants who switched from smoking conventional tobacco cigarettes to using heat-not-burn tobacco products.

6.1.2.4 Relative health-related benefits associated with heat-not-burn tobacco products

The authors of the mapped studies reported no absolute benefits associated with heat-not-burn tobacco products, but did report relative benefits (Table 66). For example, cardiovascular disease outcome indicators reflected more clinically favourable levels in heat-not-burn tobacco product users than those observed in conventional cigarette smokers, but less favourable than those observed in smoking abstainers. A similar picture emerged for outcomes of harmful and potentially harmful constituents in cigarette smoke. For example, lower levels of harmful and potentially harmful constituents (see listing on page 8) in cigarette smoke were observed in the urinary, plasma, or blood tissue tested after use of heat-not-burn tobacco products than in the results of comparable tests carried out on conventional cigarette smokers, but the lowest levels of these constituents were observed in persons abstaining from smoking. However, it is important to remember that this mapping exercise has not examined the long-term consequences of changes in cardiovascular indicators or the impact of exposure to various toxins in harmful and potentially harmful constituents of tobacco smoke; these measures of exposure to toxins were collected over a period of 10 days or less.

Table 65 Possible heat-not-burn tobacco product-related negative outcomes, mapped by study design and by adapted Academies of Sciences' umbrella terms

Study design by adapted Academies of Sciences' umbrella terms	Case reports	Case series	Information or surveillance system reports	Cross-sectional surveys	Case-control studies	Longitudinal cohort studies	Interventional trials
Dependence and abuse liability	No studies	No studies	No studies	Perceived stress (N=1)	No studies	No studies	Indicators of nicotine craving (N=3) Nicotine metabolites and concentration curves (N=2)
Cardiovascular diseases	No studies	No studies	No studies	No studies	No studies	No studies	Indicators of cardiovascular health (N=8)
Cancers	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Respiratory diseases	Acute eosinophilic pneumonia (N=2)	No studies	No studies	No studies	No studies	No studies	Indicators of respiratory function (N=1)
Oral diseases	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Developmental and reproductive effects	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Injuries	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Poisonings	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Exposure to heat-not-burn toxins	No studies	No studies	No studies	No studies	No studies	No studies	A range of harmful or potentially harmful smoke constituent (N=12)s

6.1.2.5 Summary statement on heat-not-burn tobacco product harms and benefits

The map of the peer-reviewed literature on heat-not-burn tobacco products reported a range of health-related outcomes covering dependence and abuse liability, two body systems (cardiovascular and respiratory), and toxicology measures arising from exposure to harmful and potentially harmful constituents in tobacco smoke. We note that the majority of trials reporting on this area have compared a small number of commercially available heat-not-burn tobacco products with a range of conventional tobacco cigarettes, both releasing varying chemical yields. In a number of trials, comparisons have also been made with persons who have abstained from smoking for the trial duration or for a period during a crossover trial. The overall conclusions of the primary study authors were that the impacts of heat-not-burn tobacco constituents measured for cardiovascular and respiratory health and well-being were less harmful than those of conventional tobacco cigarettes, but more harmful than those observed in study participants who abstained from smoking. In a similar fashion, lower levels of the measured harmful and potentially harmful constituents in cigarette smoke were present in heat-not-burn tobacco product users than in smokers of conventional tobacco cigarettes, but the lowest levels of these harmful and potentially harmful constituents were observed in study participants who abstained from smoking. However, the long-term consequences of these outcomes cannot be addressed by the study designs examined in this mapping exercise. Our findings on heat-not-burn tobacco products agreed with two recent systematic reviews, in that, the measured

harmful and potentially harmful constituent levels were lower in heat-not-burn tobacco product users relative to the conventional cigarette user and that most research on heat-not burn tobacco products was industry funded.[23 426] The review by the World Health Organization concluded the there is insufficient evidence to conclude that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. In fact, the Organization concluded that the there is insufficient evidence to deem that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes.[427] The Organization goes on to say that there are reservations, as heat-not-burn tobacco products may expose users to lower levels of some toxicants than conventional tobacco cigarettes, but they may also expose users to higher levels of other toxicants, and it is not clear how this toxicological profile transforms into short- and long-term health effects.[427]

6.2 Comparison with systematic reviews

6.2.1 E-cigarettes

We compared our findings to published reviews on the health effects of e-cigarettes. We located seven reviews that covered the general health effects of e-cigarettes.[428 429 430 431 6 426 432] Pisinger and Døssing (2014) completed a systematic review of the health effects of e-cigarettes and e-liquids based on 76 studies published before 14 August 2014 and concluded that despite the limitations of existing research, e-cigarettes cannot be considered harmless.[433] The Canadian Agency for Drugs and Technologies in Health (CADTH) completed a rapid response report in 2017 based on article summaries, titled *Electronic Cigarettes for the Reduction or Cessation of Smoking: Clinical Utility, Safety, and Guidelines*, and reported that the long-term safety of e-cigarettes is unknown.[429] The Commonwealth Scientific and Industrial Research Organisation (2018) reviewed the impacts of the use of e-cigarettes, personal vaporisers, and nicotine on individual and population health, and reported that the evidence available suggested that regular use of e-cigarettes was likely to have adverse health consequences, going on to say that there was a lack of clarity about the magnitude of adverse health effects and the quantity of e-cigarette use required to trigger adverse health effects.[430] The *Electronic Cigarettes – Task Force report from the European Respiratory Society* (2018) concluded that e-cigarette aerosol contained potentially toxic chemicals.[431] The 2018 Academies of Sciences' publication, *Public Health Consequences of E-Cigarettes*, concluded that the absolute risks of these products cannot be unambiguously determined at this time, and that the long-term health effects were not yet clear.[6] McNeil *et al.* published an evidence review of e-cigarettes and heated tobacco products in 2018; the report was commissioned by Public Health England.[426] The authors made a number of conclusions generally in favour of e-cigarettes [426] The World Health Organization's brief on e-cigarettes concluded with our findings that e-cigarettes are not harmless though the long-term effects such as disease causation and death are not studied adequately. The Organization stated that e-cigarettes "are not safe for young people, pregnant women, and adults who have never smoked."[432(p10)] They stated that "non-pregnant adult smokers who completely switch from combustible tobacco cigarettes to use of unadulterated and appropriately regulated e-cigarettes alone might reduce their health risks".[432(p10)] The complete switch is consistent with the concept that e-cigarettes have no place in smoking reduction and dual use is not beneficial to health status.

We found studies that identified an association between e-cigarette use and depression. Byrne *et al.* also highlighted the association between e-cigarette use and depression, which it stated was not thought to be causal but that it identified a population subgroup (i.e. people suffering from depression) that was vulnerable to the uptake and continued use of e-cigarettes.[430]

We found that there appears to be early evidence of e-cigarette use causing damage to cardiovascular and respiratory organs and tissue, mainly due to exposure to metals and volatile organic compounds. Byrne *et al.* reported that there was no evidence that e-cigarette use was associated with clinical cardiovascular disease, although they stated that this conclusion was mainly due to a lack of long-term studies.[430] However, Byrne *et al.* also found in vitro studies on e-cigarette vapour, liquid, and extracts that strongly indicated potential health risks, including cell death, increased oxidative stress, reduced lung function, changed inflammatory response, altered gene

expression, and increased cellular risk factors for cardiovascular disease. The World Health Organization reported that there is insufficient research to determine with certainty whether unadulterated and appropriately regulated e-cigarette use is associated with cardiovascular or lung diseases.[432] The Organization found that the main substances in the e-cigarette aerosol that raise health concern are metals and carbonyls. The types and concentrations of metals depended on the product features and inhaling patterns of use. Exposure to certain levels of some metals may cause diseases of the cardiovascular and respiratory systems in the future.[432] These findings concur with the findings presented in our research map.

We found that a small number of studies identified the presence of carcinogens for lung, oral, and oesophageal cancers, and identified biomarkers for bladder cancers. In addition, we found two case report papers describing two e-cigarette users with oral cancer that could not be attributed to another exposure. Pisinger and Døssing found that e-cigarettes contained fine or ultrafine particles, harmful metals, carcinogenic tobacco-specific nitrosamines, volatile organic compounds, and carcinogenic carbonyls; were cytotoxic; and changed gene expressions.[433] Byrne *et al.* also reported that e-cigarettes contained carcinogenic compounds, and that carcinogenic metabolites arising from e-cigarette use were present in e-cigarette users.[430] However, Byrne *et al.* stated that the risk of developing cancer or other health effects from the levels of carcinogenic compounds and carcinogenic metabolites detected was not yet known.[430] The *Electronic Cigarettes – Task Force report from the European Respiratory Society* reported that when compared to conventional tobacco cigarettes, e-cigarettes had fewer toxins and generally contained these toxins in lower concentrations.[431] However, the report's authors also stated that the long-term effects of e-cigarette use were unknown, and there was therefore no evidence that e-cigarettes were safer than conventional tobacco cigarettes in the long term and negative health effects could not be ruled out. The Academies of Sciences also reported that e-cigarette aerosol contained fewer numbers and lower levels of most toxicants than were found in smoke from conventional tobacco cigarettes.[6] The Academies of Sciences reported that laboratory tests of e-cigarette ingredients, in vitro toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be less harmful than conventional tobacco cigarettes, but cautioned that the long-term health effects of e-cigarettes were not yet clear; the World Health Organization used this evidence in their conclusions on cancer.[432] The World Health Organization shared our and other reviewers the concerns on carbonyl compounds and it concluded that they are hazardous to users.[432] For example, formaldehyde is a human carcinogen, acetaldehyde is possibly carcinogenic to humans, acrolein is a strong irritant of the respiratory system and glyoxal shows mutagenicity. However, the Organization acknowledges that the number and levels of carbonyls detected in the aerosol were lower than in smoke from combustible tobacco, but even these levels raised health concerns.[432] McNeill *et al.* reported that one assessment of the published data on emissions from conventional tobacco cigarettes and e-cigarettes calculated the lifetime cancer risks of e-cigarettes were largely under 0.5% of the risk associated with smoking cigarettes.[426] McNeil *et al.* reported that biomarkers of exposure assessed were consistent with significant reductions in harmful constituents, and for a few biomarkers, similar levels to smokers abstaining from smoking or non-smokers were observed.[426]

We reported that a small number of studies demonstrated that dual use of e-cigarettes and were more harmful than conventional tobacco cigarettes alone. McNeill *et al.* reported found one study showed no reductions across a range of biomarkers for dual users.[426] The World Health Organization[432] and Academies of Sciences[6] also addressed the issue of dual or poly use. The Academies of Sciences review concluded that there is no available evidence on whether long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke conventional tobacco cigarettes. The World Health Organization found recent evidence that suggested that dual users have a greater level of oxidative stress than smokers and that adding use of e-cigarettes to smoking may contribute to cardiac and respiratory disease health risks.[432] The organization pointed to another study that concluded dual users were not reducing exposure to harmful toxicants compared to exclusive cigarette smokers due to their continued smoking.[432]

We found that respiratory diseases (mainly injuries to the lungs and exacerbation of asthma) were associated with e-cigarette use. Pisinger and Døssing reported that experimental studies found increased airway resistance after short-term exposure.[433] Byrne *et al.* found that the use of e-

cigarettes impaired lung function, although it notes that the independent effect of e-cigarette vaping was unclear because of potential confounding by conventional cigarette smoking.[430] McNeill *et al.* reported that there have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters, but one small scale study which examined the effect of switching from smoking to vaping demonstrated some respiratory improvements.[426] The World Health Organization supports the assertions of Pisinger and Døssing and Byrne and conclude that there is moderate evidence that e-cigarette use increases cough and wheeze in adolescents and is associated with an increase in asthma exacerbations; this evidence applies to non-smokers as well as smokers.[432]

We found a large number of studies detailing poisonings (mainly nicotine and some e-liquid constituents) and injuries (mainly burns and some fractures); there were fatalities among the poisonings and respiratory disease cases, as well as long-term disability among some burn cases. Byrne *et al.* also reported that intentional or accidental ingestion of e-liquids can cause serious injury or death.[430] On the other hand, CADTH reported that potential harms occurred from acute nicotine poisoning through ingestion of the nicotine cartridge, especially in young children, but that this was uncommon. CADTH reported that the most prominent acute safety concern was from the potential for lithium battery-powered e-cigarettes to explode, causing thermal burns to the user.[429] Byrne *et al.*, like us, identified several case studies and case series reporting blast and thermal injuries that were attributed directly to e-cigarettes.[430] McNeill *et al.* also found that e-cigarettes were associated with injuries and poisonings. The World Health Organization reported that there was conclusive evidence that e-cigarette devices can explode and cause burns and blast injuries when batteries are of poor quality, stored improperly or modified by users.[432] The World Health Organization found conclusive evidence that intentional or accidental exposure to e-liquids can result in adverse health effects including death.[432]

Pisinger and Døssing raised the issue of compounds not found in conventional tobacco cigarettes, such as propylene glycol, and said that these compounds merit special attention.[433] The Academies of Sciences reported that exposure to nicotine and to toxicants from the aerosolisation of e-cigarette ingredients was dependent on user and device characteristics.[6] McNeill *et al.* reported that levels of metals identified in e-cigarette aerosol do not give rise to any significant safety concerns to date, but metal emissions, however small, are unnecessary.[426] McNeill *et al.* also reported that two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels in e-cigarette user and that e-cigarettes can release aldehydes if e-liquids are overheated.[426]

We found that hand and mouth contact with e-cigarettes was associated with harms such as dermatitis and reduced blood circulation. Byrne *et al.* also reported that case studies suggested that e-cigarette use interferes with, or delays, wound healing.[430]

We found five studies that identified the occurrence of passive nicotine intake. The *Electronic Cigarettes – Task Force report from the European Respiratory Society* identified that second-hand exposures to chemicals in e-cigarettes may represent a potential risk, especially to vulnerable populations.[431] On the contrary, McNeill *et al.* reported there were no identified health risks of passive vaping to bystanders to date.[426] The World Health Organization reported that some studies indicate that a selection of volatile organic compounds were also exhaled into the environment during e-cigarette use.[432] The Organization went on to say that passive exposure to nicotine and particulates is lower from e-cigarette aerosol compared with conventional tobacco cigarettes, but are higher than the smoke-free level recommended by the WHO Framework Convention on Tobacco Control.[432]

We identified 12 papers that covered the outbreak of lung injury associated with e-cigarettes or vaping. The World Health Organization was the only review recent enough to cover this issue and reported that up to 7 January 2020, more than 2,500 cases had been reported to CDC from 50 states in the USA, and just under 60 deaths had been confirmed in 27 states.[432] The World Health Organization stated that CDC identified the causal agent as Vitamin E acetate which is used as an additive, most notably as a thickening agent in tetrahydrocannabinol-containing e-cigarette, or vaping, products.[432]

Generally, our thematic findings align with the high-level findings of six reviews and has some contrasting findings with one systematic review. Given the time gap between the existing systematic reviews and our mapping exercise, we identified additional recent papers covering oral diseases as well as developmental and reproductive effects associated with e-cigarettes.

6.2.2 Heat-not-burn tobacco products

We compared our findings to three recent systematic reviews on heat-not-burn tobacco products.[23] [426] [427] Simonavicius *et al*.'s focus was to appraise the peer-reviewed evidence on heat-not-burn tobacco products, their second-hand emissions, and their use by humans, and to identify differences between independent and industry-funded studies. There were points of accord between their review and our mapping exercise, but also points of difference. Like Simonavicius *et al*., we examined papers reporting on heat-not-burn tobacco products in humans; however, we excluded laboratory comparison studies on heat-not-burn tobacco product mainstream smoke emission, which is the smoke a user draws in and is measured in the laboratory using standardised machine smoking regimes. Our findings aligned with those of Simonavicius *et al.* in several ways.[23] We both found that the majority of papers examined were affiliated with the tobacco industry, and we both identified a range of harmful and potentially harmful smoking-related constituents arising from the use of heat-not-burn tobacco products. We also both observed that heat-not-burn tobacco products provided similar cigarette craving-related measures to conventional tobacco cigarettes. While Simonavicius *et al*. quantified the relative levels of harmful and potentially harmful constituents in heat-not-burn tobacco product users in comparison to the levels observed among conventional cigarette smokers, we provided a narrative summary assessment.[23] Simonavicius *et al*.'s quantification of comparisons for carbon monoxide levels and of harmful and potentially harmful smoking-related constituents did, however, align with our statements that these levels were lower in heat-not-burn tobacco product users relative to those in conventional cigarette smokers. The main points of difference were that we identified an additional nine papers for consideration, and we reported on cardiovascular and respiratory outcomes. We were unable to undertake further comparisons between our two reviews, as the focus of our mapping exercise – reporting on possible harms and benefits under the Academies of Sciences' umbrella terms – deviated from the focus of Simonavicius *et al*.'s systematic review.[23]

McNeil *et al.* published an evidence review of heated tobacco products in 2018.[426] McNeill *et al.* concluded that heated tobacco products were commercially available in 27 countries in 2018. Out of 20 studies that were included in their review, 12 were funded by manufacturing companies so and so the authors stated there is a lack of independent research. We also reported a lack of independent research, but we found that 23 out of 25 trials were industry funded. Similar to our findings, McNeill *et al*. reported that studies that compared use of heated tobacco products with smoking cigarettes as per the smokers wishes consistently reported lower nicotine levels in heated tobacco product smokers relative to conventional tobacco cigarette smokers. McNeill *et al*. reported that heated tobacco product use reduced urges to smoke conventional tobacco cigarettes, but smokers consistently reported smoking heated tobacco product was less rewarding compared with smoking a cigarette, and this finding is similar to our findings.[426]

The World Health Organization concluded "there is insufficient evidence to conclude that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. In fact, there are concerns that while they may expose users to lower levels of some toxicants than conventional tobacco cigarettes, they also expose users to higher levels of other toxicants. It is not clear how this toxicological profile translates into short- and long-term health effects."[427(p8)] The World Health Organization found that the nicotine delivery profile of some IQOS heat-not-burn tobacco products approximated to that of conventional tobacco cigarettes.[427] The Organization reported, like our findings, that satisfaction is reported to be lower than for conventional tobacco products.[427]

The World Health Organization concluded that there is no available evidence as to whether heat-not-burn tobacco products use is associated with any long-term clinical outcome, positive or negative, from exposure to the mainstream emission. One Philip Morris International study claimed to the FDA that IQOS, compared to smoking a conventional cigarette, reduced biomarkers associated with endothelial dysfunction, oxidative stress, inflammation, and high-density lipoprotein and cholesterol

counts, but the World Health Organization stated that these findings were not supported in their own paper.[427]

6.3 Research gaps

The reporting framework used in this mapping exercise allows a clear view of the published, peer-reviewed, English-language research which has been undertaken to assess the impacts of e-cigarettes and heat-not-burn tobacco products on human health. The evidence map will serve as a framework for developing questions for scientific appraisal of the nature and direction of the observed relationship within different population groups and different clinical areas. The combination of the hierarchy of evidence and the adapted Academies of Sciences' umbrella terms was a very useful method for categorising the retrieved papers. Presenting the papers in this way highlights that some areas are well described using epidemiological studies, but that there is a dearth of longitudinal cohort studies with well-designed protocols that capture the true effects of e-cigarettes and heat-not-burn tobacco products. Long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of e-cigarettes and heat-not-burn tobacco products, have a positive or negative impact on later life health outcomes. The multitude of possible outcomes require targeted long-term cohort studies to answer research questions under all of the adapted Academies of Sciences' umbrella terms in order to quantify outcome-specific differences between conventional cigarette smokers, e-cigarette users, heat-not-burn tobacco product users, dual users of any combination of these product types, and non-users of any type of cigarette. In the absence of long-term studies, modelling of levels of biological markers for exposure to harmful or potentially harmful constituents in cigarette smoke may allow us to gain a preliminary understanding of some adverse effects of e-cigarettes and heat-not-burn tobacco products. At present, the USA, among other countries, is identifying the research needs, solutions, and funding requirements to progress an understanding of the health effects of e-cigarettes and heat-not-burn tobacco products. It should be noted that there may be unknown harms which are yet to be identified. Some specific research areas that need to be examined thoroughly are the effects of deposits and accumulation of toxins from e-cigarettes and heat-not-burn tobacco products on respiratory, cardiovascular, neurological, and other body tissues; this will also require long-term studies examining the incidence of degenerative diseases and cancers among e-cigarette and heat-not-burn tobacco product users. In addition, preliminary data indicate that a thorough examination of the effects of e-cigarettes and heat-not-burn tobacco products on embryos and newborns is required.

There are four areas which we believe would enhance our understanding of the impacts not only of e-cigarettes and heat-not-burn tobacco products, but also of other tobacco-related products that people can smoke, chew, or sniff.

First, the comparison populations regarding smoking-related behaviours must be clearly defined. We identified a variety of potential comparison populations, ranging from never-smokers to current non-smokers, current smokers, current e-cigarette users, or current dual or poly users of two or more tobacco-related products, but in some cases the populations for comparison were not clearly defined. The comparison study population parameters will depend on whether evidence on the absolute or relative effects of an e-cigarette or heat-not-burn tobacco product are being measured.

Second, heterogeneity in the chemical yields and in the temperature at which the tobacco is heated for both the heat-not-burn tobacco products and the comparison conventional tobacco cigarettes needs to be closely examined and more clearly delineated in order to detect meaningful findings. There is a wide range of heat-not-burn tobacco products on the market. In general, these are known by their trade name and version (for example, THS 1.0 or THS 2.1). However, differences in chemical composition and even in certain design aspects can potentially mean that intra-brand differences between products may be similar to or even greater than inter-brand differences. In order to better assess the differences, if any, between the various heat-not-burn tobacco products and the comparison conventional tobacco cigarettes, research should take account of each product's chemical composition and levels rather than simply the brands and versions, as this would represent a more meaningful evaluation. Brand comparison represents a marketing evaluation, but chemical and design

comparison more closely aligns with a robust scientific evaluation of the products' impact on health. From this mapping exercise, it appeared that marketing techniques were employed to suggest that differences in product type affected the harms and benefits arising from the use of the various tobacco products tested. This may indeed be the case; however, without a rigorous profiling of the chemical yield of each product, differences in the products tested and their mode of use will confound any true differences in effect. The current variety of e-cigarette devices and the chemical composition of the various e-liquids available on the market needs to be documented and evaluated in order to determine the safety of these products. The use of e-liquids as a carrier substance for psychoactive drugs, both licit and illicit, also needs to be investigated. In addition, the overlap between e-cigarette use and the use of other psychoactive drugs, including alcohol, requires examination. When considering young people, the use of flavourings to entice non-smokers to initiate e-cigarette use and the issue of flavourings approved for ingestion, but not for inhalation, requires investigation.

Third, what, if any, difference changes in levels of biomarkers of exposure to harmful or potentially harmful vapour or smoke constituents have on the subsequent development of associated deleterious outcomes needs to be understood. Heat-not-burn tobacco products and e-cigarettes have been reported to deliver lower levels of the measured chemical toxicants than conventional tobacco cigarettes, while at the same time effectively delivering comparable levels of nicotine. This duality has been purported to offer a more benign exposure to the adverse health effects of conventional tobacco cigarettes and, in some way, to represent a less harmful nicotine addiction behaviour. However, the chemical components of all tobacco-related products represent an array of harmful and potentially harmful substances linked to adverse health outcomes for a range of body systems, such as cardiovascular, respiratory, and even neurological systems, as well as an array of diseases, such as cancers of the mouth, lungs, and bladder. A better understanding of the direct, mechanistic, and parallel effects of these toxins is required before assertions can be made that lower levels of exposure translate into reductions in the incidence of specific or overall disease outcomes. In addition, other harmful materials (e.g. metals) not currently in conventional tobacco cigarettes are present in the promoted tobacco-consumption substitutes, including e-cigarettes and heat-not-burn products. Furthermore, regarding nicotine uptake, what, if any, benefit arises from substituting one mode of delivery (conventional tobacco cigarettes) with another (e-cigarettes or heat-not-burn tobacco products) requires consideration, especially if the nicotine dependence habit remains unchanged or a dual habit develops.

Fourth, there is a dearth of longitudinal information on specific populations where evidence on the impact of e-cigarettes could clearly contribute to public health policy formation. These populations include: adolescents, pregnant and lactating women and pregnancy itself (embryos and newborns), people with mental health problems, as well as patients with cancer, cardiovascular disease, or diabetes.

6.4 Strengths and limitations

The combination of the hierarchy of evidence and the adapted Academies of Sciences' framework was a very useful method for categorising the existing literature. We have categorised 388 studies examining the possible harms and benefits of e-cigarettes and heat-not-burn tobacco products on human health. This mapping exercise allows us to identify the indicative benefits and harms, but does not allow us to explore any subject area in depth. While we can describe heterogenous findings, this exercise does not allow us to investigate the potential underlying reasons for the heterogeneity. Due to time and other resource limitations, we concentrated on human studies as these were the priority for this brief and excluded papers examining the effects of e-cigarettes and heat-not-burn tobacco products in animal studies and environmental studies. We suggest that an updated mapping exercise be completed in these areas in the near future, as systematic reviews identified that e-cigarettes are associated with some harms in animals.[430 431 6] We anticipate that this mapping exercise will help subject-specific researchers determine what was known by November 2019 in their area of study and move quickly to address primary research gaps. With the exception of the trials, the observational epidemiological studies included in the evidence map can only provide associations between e-

cigarettes and heat-not-burn tobacco products with adverse health effects, rather than demonstrate causal links, and this is indicative of low levels of evidence.

A limitation of all mapping exercises is that quality assessment of each primary paper is not required which prohibits critical examination of the primary authors' study findings. While we did not do a quality assessment of each paper, we did categorise the studies by study design as rated on a hierarchy of evidence. Furthermore, we presented the study definition and purpose with respect to causal inferences in the findings' chapters. Validity was also assessed by highlighting small sample sizes, loss to follow-up, lack of clarity with respect to exposures or interventions, lack of clarity with respect to comparison groups, and lack of independence with respect to tobacco industry funding. In addition, we have classified intervention trials by their level of randomisation. However, it is important to note that inclusion of a study in this or any other mapping exercise does not indicate that the identified relationship or the reported primary papers authors' assertions are valid, as we have not critically appraised the individual studies. In addition, we cannot comment on the the strength of the reported evidence.

A serious limitation of any systematic review of these products is that 'e-cigarettes', 'e-liquids', and 'heat-not-burn tobacco products' are broad terms for a miscellaneous group of products that change over time and between brands, and the research is not generalisable beyond the specific products tested. In addition, very few heat-not-burn tobacco products and e-cigarettes have published, peer-reviewed test results, and new products are being developed as we write. The predominance of the tobacco industry in leading the research on heat-not-burn tobacco products, and its influence on research on e-cigarettes, are also concerns, as are the focus, the nature, and the very short time span over which such products have been studied. In the short-term trials, heat-not-burn tobacco product use and e-cigarette use were reported to result in disturbances to health, e.g. cardiovascular and respiratory markers of well-being, and raised levels of biomarkers of exposure to harmful or potentially harmful smoke constituents. Such constituents were observed in studies of conventional tobacco cigarettes and were known to be harmful to health.[411] However, several factors (listed in Section 6.3) must be accounted for before evidence regarding the harmful or beneficial nature of heat-not-burn tobacco products or e-cigarettes and their longer-term impact can be fully evaluated. The health-related outcomes grouped as harms and benefits spanned a wide range of biological measures, from transient indicators of changes in biological cells and tissue to full blown pathological diseases. However, whether the observed outcome associated with the exposure represented a harm or a benefit depended not only on consideration of the temporal exposure-outcome relationship, but on the health-related behaviours of the study population.This project has identified numerous morbidities, possibly associated with exposure to e-cigarettes or heat-not-burn tobacco products. However, an important point of note is that the effect, whether an absolute or relative harm or benefit of e-cigarette exposure, differed not only according to the underlying conventional tobacco smoking-related characteristics of the study populations, but also according to the product and the outcomes being assessed. Interpretation of the effect of e-cigarettes requires findings from not just a range of individual questions on specific exposure-outcome relationships, but also aggregation of the range exposure-outcome relationships. For instance, examining the impact of nicotine in relation to issues of dependence and abuse represents one potential exposure-outcome relationship of interest. In a well-designed and conducted study, findings will inform understanding of nicotine dependency, but these findings will not necessarily inform understanding of other pathologies arising from e-cigarette use. Understanding harms or benefits arising from nicotine uptake requires not just framing findings taking account of the baseline smoking-related behaviours of the population, but also taking account of the relationships between e-cigarette exposure and each of the other human body systems be it at the level of genes, cellular tissues, or organs.

An area touched on in the mapping exercise is the varying levels of detail by which e-cigarette or heat-not-burn product use was recorded. Study authors used a variety of questions to gather data on the use of e-cigarettes, conventional tobacco cigarettes, and other tobacco-related products. The depth of reporting varied ranging from binary (yes, no) variables recording current use to composite variables recording the best practice variable 'pack years' (number of units used per day- and number of years of product use). In some cases, one of the following data measures were collected: type of product, strength of product, and puff topography. Puff topography, usually measured in a laboratory

setting, is commonly used to assess nicotine self-administration in cigarette smokers, and involves measuring variables such as puff volume, duration, number of puffs per product, and interval between puffs. Puff length in e-cigarette users varies with experience, more experienced users usually take longer puffs. The more detailed measures of use provide a more accurate assessment of exposure and thus reduce the level of residual confounding arising from inadequate assessment of exposure. However, heterogeneity in data gathering practices reduces comparability of findings even among studies addressing the same scientific question and weakens the accuracy of statistical quantification of effect.

Information system coding processes have been expanded to include e-cigarette-related health conditions, although they need further expansion in order to code the newly observed harms arising from e-cigarette and heat-not-burn tobacco product use. Authors from some of the included papers note that adverse events may be under-reported due to surveillance system coding deficiencies. The number of cases categorised under ‘other outcomes’ highlights that the Academies of Sciences’ framework headings will need to be expanded as we learn more about the harms and benefits of e-cigarettes and heat-not-burn tobacco products. It may be useful to add five new headings to the Academies of Sciences’ framework headings: ‘endocrine diseases’, ‘neurological diseases’, ‘ophthalmic diseases’, ‘exposure to e-cigarette toxins’ and ‘second- and third-hand effects of e-cigarette toxin and toxicant uptake’; second- and third-hand effects of e-cigarette toxin would outline the effects of involuntary exposure under a separate heading.

Conclusion

The e-cigarette-related health harms, harm reduction, and benefits known to date are presented in this mapping exercise. However, there may be unknown harms. Most of the observed clinical harms were due to acute harmful events associated with the use of e-cigarettes and were reported in descriptive case studies, surveillance system papers, and cross-sectional survey papers.

The acute harms included poisonings (mainly nicotine and some e-liquid constituents), injuries (mainly burns and some fractures), and respiratory diseases (mainly injuries to the lungs and exacerbation of asthma). There were fatalities among the poisonings and respiratory disease cases, and long-term disability among some burn cases. Both the poisoning cases and the respiratory disease cases highlighted a possible association between e-cigarettes and the use of other drugs such as alcohol, synthetic cannabinoids, and opiates.

There was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds. Four cross-sectional surveys on cancers identified the presence of carcinogens for lung, oral, and oesophageal cancer, and one identified biomarkers for bladder cancers. Some respiratory, cardiovascular, and oral diseases were noted to be less harmful in e-cigarette users than in conventional cigarette smokers, but were as harmful as in dual users (i.e. users of both conventional tobacco cigarettes and e-cigarettes). However, these respiratory, cardiovascular, and oral diseases findings were not consistent across all studies.

The evidence map featured few benefits reported in the examined studies on the harms and benefits associated with e-cigarettes. The most common benefits reported by a small number of heavy smokers of conventional tobacco cigarettes was smoking cessation or reduction in smoking. We note that many studies showed that dual use (of both e-cigarettes and conventional tobacco cigarettes) was not less harmful than smoking conventional tobacco cigarettes alone, thereby raising questions about the smoking reduction benefit of e-cigarettes. Alongside this map, two systematic reviews [424] [425] on e-cigarettes were completed by the HRB. In the first review, we found that e-cigarettes were not more effective for smoking cessation than approved nicotine replacement therapies (NRTs), which questions the need for e-cigarettes as a smoking cessation intervention. In the second review, we found that e-cigarettes were associated with initiation of conventional cigarette smoking among adolescents, which identifies a potentially serious harm.

Generally, our thematic findings align with the high-level findings of six reviews and have some contrasting findings with one systematic review. Given the time gap between the existing systematic reviews and our mapping exercise, we identified additional recent papers covering oral diseases, and developmental and reproductive effects associated with e-cigarettes.

Long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of heat-not-burn tobacco products and e-cigarettes, have a positive or negative impact on later life health outcomes.

The map of the peer-reviewed literature on heat-not-burn tobacco products reported a range of health-related outcomes covering dependence and abuse liability, two body systems (cardiovascular and respiratory), and toxicology measures arising from exposure to harmful and potentially harmful constituents in tobacco smoke.

We note that the majority of trials reporting on this area have compared a small number of commercially available heat-not-burn tobacco products with a range of conventional tobacco cigarettes, both releasing varying chemical yields. In a number of trials, comparisons have also been made with persons who have abstained from smoking for the trial duration or for a period during a crossover trial. This mapping project has identified that the overall conclusion of the study authors was that the impacts of heat-not-burn tobacco constituents measured for cardiovascular and respiratory health and well-being were less harmful than those of conventional tobacco cigarettes, but more harmful than those observed in study participants who abstained from smoking. In a similar fashion, lower levels of the measured harmful and potentially harmful constituents in cigarette smoke were present in heat-not-burn tobacco product users than in smokers of conventional tobacco

cigarettes, but the lowest levels of these harmful and potentially harmful constituents were observed in study participants who abstained from smoking. However, the long-term consequences of these outcomes cannot be addressed by the study designs examined in this mapping exercise.

Our findings on heat-not-burn tobacco products agreed with two recent systematic reviews, in that, the measured harmful and potentially harmful constituent levels were lower in heat-not-burn tobacco product users relative to the conventional cigarette user and that most research on heat-not burn tobacco products was industry funded. The review by the World Health Organization concluded the there is insufficient evidence to conclude that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. In fact, the Organization concluded that the there is insufficient evidence to deem that heat-not-burn tobacco products are less harmful than conventional tobacco cigarettes. The Organization goes on to say that there are reservations, as heat-not-burn tobacco products may expose users to lower levels of some toxicants than conventional tobacco cigarettes, but they may also expose users to higher levels of other toxicants, and it is not clear how this toxicological profile transforms into short- and long-term health effects.

References

1. Adriaens K, Gucht DV, Baeyens F. IQOS(TM) vs. e-cigarette vs. tobacco cigarette: a direct comparison of short-term effects after overnight-abstinence. *Int J Environ Res Public Health* 2018;15(12):pii: E2902. doi: 10.3390/ijerph15122902
2. Department of Health, Ireland,. Tobacco free Ireland. Report of the Tobacco Policy Review Group Dublin, Ireland: Department of Health,; 2013 [Available from: https://assets.gov.ie/19465/0c99a96e05c54b249c7d53b93b17437c.pdf.
3. Zhu S-H, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control* 2014;23:iii3-iii9. doi: 10.1136/tobaccocontrol-2014-051670
4. Hsu G, Sun JY, Zhu S-H. Evolution of electronic cigarette brands from 2013-2014 to 2016-2017: analysis of brand websites. *J Med Internet Res* 2018;20(3):e80. doi: 10.2196/jmir.8550
5. National Institute on Drug Abuse. Vaping devices (electronic cigarettes) Maryland, USA: NIH National Institute on Drug Abuse; 2020 [updated January 2020; cited 2020 08 February 2020]. Website]. Available from: https://www.drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes accessed 08 February 2020 2020.
6. National Academies of Sciences Engineering M. Public health consequences of e-cigarettes. Washington DC, USA: The National Academies Press; 2018 [774pp]. Available from: https://dx.doi.org/10.17226/24952.
7. Elias J, Ling PM. Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products. *Tob Control* 2018;27(Suppl 1):s96. doi: 10.1136/tobaccocontrol-2018-054433
8. Slade J, Connolly GN, Lymperis D. Eclipse: Does it live up to its health claims? *Tob Control* 2002;11(suppl 2):ii64. doi: 10.1136/tc.11.suppl_2.ii64
9. World Health Organization. Heated tobacco products (HTPs) market monitoring information sheet [website] Geneva, Switzerland: World Health Organization (WHO) 2018a [Available from: https://www.who.int/tobacco/publications/prod_regulation/htps-marketing-monitoring/en/ accessed 11 Jan 2020.
10. Kim M. Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea. *Tob Control* 2018;27(e1):e76. doi: 10.1136/tobaccocontrol-2017-053965
11. Caputi TL. Industry watch: heat-not-burn tobacco products are about to reach their boiling point. *Tob Control* 2017;26(5):609. doi: 10.1136/tobaccocontrol-2016-053264
12. British American Tobacco. Tobacco heating products[website]: British American Tobacco,; 2020 [Available from: https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWUGNJ.
13. Scott P. 2 Stanford grads stoked a billion-dollar industry with Juul. Now their vaping company is under fire[webpage]. *Stanford Daily* 2019 26 Sep 2019.
14. Japan Tobacco Inc. Ploom and seven different packs of Ploom tobacco pods to go on sale in on 12 December 2013 [website]: Japan Tobacco Inc.,; 2013 [Available from: https://www.jt.com/media/news/2013/1128_01.html
15. Lopez AA, Hiler M, Maloney S, et al. Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers. *Drug Alcohol Depend* 2016;169:33-40. doi: 10.1016/j.drugalcdep.2016.10.005
16. Japan Tobacco Inc. Ploom TECH, a new state-of-the-art tobacco vaporizer to be launched online nationally and at certain stores in Fukuoka City, from early March [website] Japan Tobacco Inc.,; 2016 [Available from: https://www.jt.com/media/news/2016/0126_01.html.
17. Kyoung-Son S. KT&G introduces the first Korean heat-not-burn cigarette. *Korea JoongAng Daily* 2017 08 Nov 2017.
18. Imperial Brands. Next generation products [website] 2020 [Available from: https://www.imperialbrandsplc.com/about-us/next-generation-products.html
19. Committees on toxicity camocif, consumer products and the environment,. Toxicological evaluation of novel heat-not-burn tobacco products – non-technical summary: Committees on toxicity, carcinogenicity and mutagenicity of chemicals in food, consumer products and the environment,; 2017 [Available from: https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_summary.pdf
20. Mallock N, Pieper E, Hutzler C, et al. Heated tobacco products: A review of current knowledge and initial assessments. *Front Public Health* 2019;7:287. doi: 10.3389/fpubh.2019.00287
21. Dautzenberg B, Dautzenberg MD. Le tabac chauffé: Revue systématique de la littérature. *Rev Mal Respir* 2019;36(1):82-103. doi: 10.1016/j.rmr.2018.10.010
22. Biondi-Zoccai G, Sciarretta S, Bullen C, et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 randomized trial. *J Am Heart Assoc* 2019;8(6):e010455. doi: 10.1161/JAHA.118.010455 [published Online First: 16 Mar 2019]

23. Simonavicius E, McNeill A, Shahab L, et al. Heat-not-burn tobacco products: A systematic literature review. *Tob Control* 2019;28:582-94. doi: 10.1136/tobaccocontrol-2018-054419 [published Online First: 23 Aug 2019]
24. Ratajczak A, Jankowski P, Strus P, et al. Heat not burn tobacco product—a new global trend: Impact of heat-not-burn tobacco products on public health, a systematic review. *Int J Environ Res Public Health* 2020;17(2):E409. doi: 10.3390/ijerph17020409
25. European Union. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. *Official Journal of the European Union* 2014;57(L127):1-38.
26. Health Service Executive (HSE). Tobacco products directive Dublin, Ireland: Health Service Executive; 2018 [updated 2018. Website]. Available from: https://www.hse.ie/eng/about/who/tobaccocontrol/tobaccoproductdirective/ accessed 08 February 2020 2020.
27. Porta M. A dictionary of epidemiology: Online Oxford: Oxford University Press; 2014 [updated 2014. 5:[Webpage]. accessed 01 September 2019 2019.
28. Bradford Hill A. The environment and disease: Association or causation? *Proc R Soc Med* 1965;58:295-300.
29. World Health Organization. Classifications Geneva, Switzerland: World Health Organization,; 2018b [updated 18 Jun 2018. Webpage]. Available from: https://www.who.int/classifications/icd/en/ accessed 01 Sep 2019 2019.
30. Medical Dictionary for Regulatory Activities. MedDRA hierarchy. Basics. How to use Virginia, USA: Medical Dictionary for Regulatory Activities; 2019 [updated Not recorded. Website]. Available from: https://www.meddra.org/how-to-use/basics/hierarchy accessed 01 September 2019 2019.
31. EPPI-Reviewer 4.0: software for research synthesis. EPPI-Centre Software. [program]. London: Social Science Research Unit, Institute of Education, University of London., 2010.
32. McGowan J, Sampson M, Salzwedel DM, et al. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40-46. doi: 10.1016/j.jclinepi.2016.01.021
33. Koster J. Pubmed PubReminer Amsterdam, The Netherlands: Academisch Medisch Centrum, Universiteitvan Amsterdam; 2019 [Available from: https://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi.
34. Monroy AE, Hommel E, Smith ST, et al. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. *Clin Geriatr* 2012;20(3):28-32.
35. Ahmed N, Kalininskiy A, Gandhi H, et al. Spontaneous coronary artery dissection in a postpartum e-cigarette smoker. *BMJ Case Rep* 2018;2018:bcr-2018-225194. doi: 10.1136/bcr-2018-225194 [published Online First: 04 Jun 2018]
36. Thota D, Latham E. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. *J Emerg Med* 2014;47(1):15-17. doi: 10.1016/j.jemermed.2013.09.034
37. Hureaux J, Drouet M, Urban T. A case report of subacute bronchial toxicity induced by an electronic cigarette. *Thorax* 2014;69(6):596-97. doi: 10.1136/thoraxjnl-2013-204767
38. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary lipid-laden macrophages and vaping. *N Engl J Med* 2019;381:1488-89. doi: 10.1056/NEJMc1912038 [published Online First: 10 Oct 2019]
39. Nair N, Hurley M, Gates S, et al. Life-threatening hypersensitivity pneumonitis secondary to e-cigarettes. *Arch Dis Child* 2019;11 doi: 10.1136/archdischild-2019-317889 [published Online First: 11 Nov 2019]
40. Agustin M, Yamamoto M, Cabrera F, et al. Diffuse alveolar hemorrhage induced by vaping. *Case Rep Pulmonol* 2018;2018:9724530. doi: 10.1155/2018/9724530 [published Online First: 07 Ju 2018]
41. Macedonia TV, Krefft SD, Rose CS. Persistent severe fixed airways obstruction in a high-dosing e-cigarette user. *J Gen Intern Med* 2019;35(1):345-49. doi: 10.1007/s11606-019-05462-0
42. Flower M, Nandakumar L, Singh M, et al. Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. *Respirol Case Rep* 2017;5(3):e00230. doi: 10.1002/rcr2.230
43. Marasco RD, Loizzi D, Ardo NP, et al. Spontaneous pneumomediastinum after electronic cigarette use. *Ann Thorac Surg* 2018;105(6):e269-e71. doi: 10.1016/j.athoracsur.2017.12.037
44. Bonilla A, Blair AJ, Alamro SM, et al. Recurrent spontaneous pneumothoraces and vaping in an 18-year-old man: A case report and review of the literature. *J Med Case Rep* 2019;13(1):283. doi: 10.1186/s13256-019-2215-4 [published Online First: 09 Sept 2019]
45. Dicpinigaitis PV, Trachuk P, Fakier F, et al. Vaping-associated acute respiratory failure due to acute lipoid pneumonia. *Lung* 2020;198(1):31-33. doi: 10.1007/s00408-019-00277-6
46. Ocampo-Gonzalez FA, Park JW. Cytologic features of vaping-induced lung injury: A case report. *Diagn Cytopathol* 2020;48(2):174-76. doi: 10.1002/dc.24343
47. Sechrist JW, Kanne JP. Vaping-associated lung disease. *Radiology* 2019;294(1):18. doi: 10.1148/radiol.2019192073 [published Online First: 05 Nov 2019]

48. Arter ZL, Wiggins A, Hudspath C, et al. Acute eosinophilic pneumonia following electronic cigarette use. *Respir Med Case Rep* 2019;27:100825. doi: 10.1016/j.rmcr.2019.100825 [published Online First: 18 Mar 2019]
49. McCauley L, Markin C, Hosmer D. An unexpected consequence of electronic cigarette use. *Chest* 2012;141(4):1110-13. doi: 10.1378/chest.11-1334
50. Sommerfeld CG, Weiner DJ, Nowalk A, et al. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. *Pediatrics* 2018;141(6):e20163927. doi: 10.1542/peds.2016-3927
51. Bakre SA, Al-Farra TS, Al-Farra S. Diffuse alveolar damage and e-cigarettes: Case report and review of literature. *Respir Med Case Rep* 2019;28:100935. doi: 10.1016/j.rmcr.2019.100935 [published Online First: 24 Sept 2019]
52. Twohig P, Rivington J, Cook W. Are e-cigarettes the answer? A novel case of methemoglobinemia. *Am J Med* 2019;132(8):e648-e49. doi: 10.1016/j.amjmed.2019.02.051
53. Ring Madsen L, Vinther K, Niels H, et al. A cancer that went up in smoke: Pulmonary reaction to e-cigarettes imitating metastatic cancer. *Chest* 2016;149(3):e65-67. doi: 10.1016/j.chest.2015.09.003
54. Carter T, Tucker D, Kilic A, et al. Life-threatening vesicular bronchial injury requiring veno-venous extracorporeal membrane oxygenation rescue in an electronic nicotine delivery system user. *Clin Pract Cases Emerg Med* 2017;1(3):212-17. doi: 10.5811/cpcem.2017.3.33171
55. Viswam D, Trotter S, Burge PS, et al. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. *BMJ Case Rep* 2018;2018:bcr-2018-224350. doi: 10.1136/bcr-2018-224350 [published Online First: 06 Jul 2018]
56. Miler JA, Hajek P. Resolution of recurrent tonsillitis in a non-smoker who became a vaper. A case study and new hypothesis. *Med Hypotheses* 2017;109:17-18. doi: 10.1016/j.mehy.2017.09.006 [published Online First: 11 Sep 2017]
57. Khan MS, Khateeb F, Akhtar J, et al. Organizing pneumonia related to electronic cigarette use: A case report and review of literature. *Clin Respir J* 2018;12(3):1295-99. doi: 10.1111/crj.12775
58. Miler JA, Hajek P. Resolution of chronic nasal Staphylococcus aureus infection in a non-smoker who started to use glycerine based e-cigarettes: Antibacterial effects of vaping? *Med Hypotheses* 2018;118:42-43. doi: 10.1016/j.mehy.2018.05.011 [published Online First: 15 May 2018]
59. Farinha H, Martins V. Lingua villosa nigra associated with the use of electronic cigarette. *Acta Med Port* 2015;28(3):393.
60. Bartram A, Jones N, Endersby S. Lichenoid eruption associated with use of an e-cigarette. *Br J Oral Maxillofac Surg* 2016;54(4):475. doi: 10.1016/j.bjoms.2015.06.003
61. St Claire C, Ashack KA, Liss W, et al. An asymptomatic hyperpigmented tongue. *J Am Acad Dermatol* 2017;76(4):e115-16. doi: 10.1016/j.jaad.2016.09.010
62. Lilleker R. Dear editor. *Dent Update* 2017;43(9):893-94. doi: 10.12968/denu.2016.43.9.893
63. Jablow LM, Sexton RJ. Spontaneous electronic cigarette explosion: A case report. *J Med Case Rep* 2015;3(4):93-94. doi: 10.12691/ajmcr-3-4-1
64. Goverman J, Schulz JT. Thigh burns from exploding e-cigarette. *Burns* 2016;42(7):1618. doi: 10.1016/j.burns.2016.07.024
65. Walsh K, Sheikh Z, Johal K, et al. Rare case of accidental fire and burns caused by e-cigarette batteries. *BMJ Case Rep* 2016;2016:bcr2015212868. doi: 10.1136/bcr-2015-212868
66. Anderson H, Richie C, Bernard A. A surprisingly volatile smoking alternative: explosion and burns as risks of e-cigarette use. *J Burn Care Res* 2017;38(5):e884. doi: 10.1097/BCR.0000000000000454
67. Serror K, Chaouat M, De Runz A, et al. Thigh deep burns caused by electronic vaping devices (e-cigarettes): A new mechanism. *Burns* 2017;43(5):1133-35. doi: 10.1016/j.burns.2017.01.038
68. Shastry S, I. LM. Electronic vapor cigarette battery explosion causing shotgun-like superficial wounds and contusion. *West J Emerg Med* 2016;17(2):177-80. doi: 10.5811/westjem.2016.1.29410
69. Benowitz N. E-cigarette explosion in a patient room Rockville, Maryland: AHRQ Patient Safety Network; 2019 [updated 2019; cited 2020. April 2019:[AHRQ Patient Safety Network (PSNet) is a national web-based resource featuring the latest news and essential resources on patient safety.]. Available from: https://psnet.ahrq.gov/webmm/case/474 accessed 13 January 2020.
70. Jamison A, Lockington D. Ocular chemical injury secondary to electronic cigarette liquid misuse. *JAMA Ophthalmol* 2016;134(12):1443. doi: 10.1001/jamaophthalmol.2016.3651
71. McCague Y. Ocular chemical burns secondary to accidental administration of e-cigarette liquid. *Adv Emerg Nurs J* 2018;40(2):104-09. doi: 10.1097/TME.0000000000000183
72. Archambeau BA, Young S, Lee C, et al. E-cigarette blast injury: complex facial fractures and pneumocephalus. *West J Emerg Med* 2016;17(6):805-07. doi: 10.5811/westjem.2016.7.31354
73. Brooks JK, Kleinman JW, Brooks JB, et al. Electronic cigarette explosion associated with extensive intraoral injuries. *Dent Traumatol* 2017;33(2):149-52. doi: 10.1111/edt.12293
74. Katz MG, Russell KW. Injury from e-cigarette explosion. *N Engl J Med* 2019;380(25):2460. doi: 10.1056/NEJMicm1813769

75. Norii T, Plate A. Electronic cigarette explosion resulting in a C1 and C2 fracture: A case report. *J Emerg Med* 2017;52(1):86-88. doi: 10.1016/j.jemermed.2016.08.010 [published Online First: 04 Oct 2016]
76. Khairudin MN, Mohd Z, Aida Z, et al. Front to back ocular injury from a vaping-related explosion. *BMJ Case Rep* 2016;2016:bcr2016214964. doi: 10.1136/bcr-2016-214964
77. Vaught B, Spellman J, Shah A, et al. Facial trauma caused by electronic cigarette explosion. *Ear Nose Throat J* 2017;96(3):139-42. doi: 10.1177/014556131709600314 [published Online First: 01 Mar 2017]
78. Moore J, Mihalache G, Messahel A. "Exploding" electronic cigarette: A case report. *Br J Oral Maxillofac Surg* 2016;54(9):1056-57. doi: 10.1016/j.bjoms.2016.05.020
79. Ban C, Krishnan DG, Abdallah Y. Ballistic trauma from an exploding electronic cigarette: Case report. *Oral Maxillofac Surg Case* 2017;3(3):61-63. doi: 10.1016/j.omsc.2017.01.007
80. Foran I, Oak NR, Meunier MJ. High-pressure injection injury caused by electronic cigarette explosion: A case report. *JBJS Case Connect* 2017;7(2):e36. doi: 10.2106/JBJS.CC.16.00177
81. Satteson ES, Walker NJ, Tuohy CJ, et al. Extensive hand thermal and blast injury from electronic cigarette explosion: A case report. *Hand (N Y)* 2017;13(3):NP1–NP5. doi: 10.1177/1558944717744333 [published Online First: 01 Dec 2017]
82. Ackley E, B. WJT, Kunrath C, et al. Too hot to handle? When vaporizers explode. *J Pediatr* 2018;196:320-20.e1. doi: 10.1016/j.jpeds.2017.12.032
83. Cason DE, Morgan DE, Pietryga JA. Injuries from an exploding e-cigarette: A case report. *Ann Intern Med* 2016;165(9):678-79. doi: 10.7326/L16-0023
84. Harrison R, Hicklin Jr. D. Electronic cigarette explosions involving the oral cavity. *J Am Dent Assoc* 2016;147(11):891-96. doi: 10.1016/j.adaj.2016.03.018
85. Roger JM, Abayon M, Elad S, et al. Oral trauma and tooth avulsion following explosion of e-cigarette. *J Oral Maxillofac Surg* 2016;74(6):1181-85. doi: 10.1016/j.joms.2015.12.017
86. Cant A, Collard B, Cunliffe D. Electronic cigarettes: Necrotic ulcer. *Br Dent J* 2017;222(4):226. doi: 10.1038/sj.bdj.2017.150
87. Andresen NS, Lee DJ, Kowalski CE, et al. Fall with e-cigarette in mouth resulting in pharyngeal and esophageal burns. *JAMA Otolaryngol Head Neck Surg* 2018;144(4):385-86. doi: 10.1001/jamaoto.2017.3265
88. Chi AC, Neville BW, Ravenel M. Electronic cigarette explosion: Case report of an emerging cause of orofacial trauma. *Trauma* 2018;20(1):62-67. doi: 10.1177/1460408616674234 [published Online First: 16 Oct 2014]
89. Hassan S, Anwar MU, Muthayya P, et al. Burn injuries from exploding electronic cigarette batteries: An emerging public health hazard. *J Plast Reconstr Aesthet Surg* 2016;69(12):1716-18. doi: 10.1016/j.bjps.2016.09.014
90. Bohr S, Almarzouqi F, Pallua N. Extensive burn injury caused by fundamental electronic cigarette design flaw. *Ann Burns Fire Disasters* 2016;29(3):231-33.
91. Thornton SL, Oller L, Sawyer T. Fatal intravenous injection of electronic nicotine delivery system refilling solution. *J Med Toxicol* 2014;10(2):202-04. doi: 10.1007/s13181-014-0380-9
92. Eberlein CK, Frieling H, Kohnlein T, et al. Suicide attempt by poisoning using nicotine liquid for use in electronic cigarettes. *Am J Psychiatry* 2014;171(8):891. doi: 10.1176/appi.ajp.2014.14030277
93. Schipper EM, de Graaff LCG, Koch BCP, et al. A new challenge: Suicide attempt using nicotine fillings for electronic cigarettes. *Br J Clin Pharmacol* 2014;78(6):1469-71. doi: 10.1111/bcp.12495
94. Chen BC, Bright SB, Trivedi AR, et al. Death following intentional ingestion of e-liquid. *Clin Toxicol (Phila)* 2015;53(9):914-16. doi: 10.3109/15563650.2015.1090579
95. Martin-Kleisch A, Leclercq M, Zulfiqar AA. Voluntary e-liquid's intoxication. *Annales Francaises de Medecine d'Urgence* 2016;6(6):428-30. doi: 10.1007/s13341-016-0688-y
96. Belkoniene M, Socquet J, Njemba-Freiburghaus D, et al. Near fatal intoxication by nicotine and propylene glycol injection: A case report of an e-liquid poisoning. *BMC Pharmacol Toxicol* 2019;20:28. doi: 10.1186/s40360-019-0296-8 [published Online First: 10 May 2019]
97. Gupta S, Gandhi A, Manikonda R. Accidental nicotine liquid ingestion: emerging paediatric problem. *Arch Dis Child* 2014;99(12):1149. doi: 10.1136/archdischild-2014-306750
98. Eggleston W, Nacca N, Stork CM, et al. Pediatric death after unintentional exposure to liquid nicotine for an electronic cigarette. *Clin Toxicol (Phila)* 2016;54(9):890-91. doi: 10.1080/15563650.2016.1207081
99. Gomolka E, Radomska M, Bielska DE. Ostre zatrucie płynem do e-papierosów – opis przypadku [Acute poisoning with e-cigarette liquid - case report]. *Przegl Lek* 2016;73(10):795-97.
100. Rogers JS, Rehrer SJ, Hoot NR. Acetylfentanyl: An emerging drug of abuse. *J Emerg Med* 2016;50(3):433-36. doi: 10.1016/j.jemermed.2015.10.014
101. Seo AD, Kim DC, Yu HJ, et al. Accidental ingestion of e-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. *Korean J Pediatr* 2016;59(12):490-93. doi: 10.3345/kjp.2016.59.12.490

102. Waldman W, Sein AJ. Nagle zatrzymanie krazenia w przebiegu zatrucia nikotyna--opis przypadku i przeglad pismiennictwa [Cardiac arrest during intoxication with nicotine--a case report and a review of literature] *Przegl Lek* 2012;69(8):606-08.
103. Bartschat S, Mercer-Chalmers-Bender K, Beike J, et al. Not only smoking is deadly: Fatal ingestion of e-juice-a case report. *Int J Legal Med* 2015;129(3):481-86. doi: 10.1007/s00414-014-1086-x
104. Garat A, Nisse P, Kauv M, et al. Lactic acidosis due to voluntary e-liquid ingestion. *Toxicologie Analytique et Clinique* 2016;28(4):329-32. doi: 10.1016/j.toxac.2016.05.001
105. You G, Rhee J, Park Y, et al. Determination of nicotine, cotinine and trans-3'-hydroxycotinine using LC/MS/MS in forensic samples of a nicotine fatal case by oral ingestion of e-cigarette liquid. *J Forensic Sci* 2016;61(4):1149-54. doi: 10.1111/1556-4029.13083
106. Lam RPK, Tang MHY, Leung SC, et al. Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative analysis of serum drug concentrations. *Clin Toxicol (Phila)* 2017;55(7):662-67. doi: 10.1080/15563650.2017.1307385
107. Morley S, Slaughter J, Smith PR. Death from ingestion of e-liquid. *J Emerg Med* 2017;53(6):862-64. doi: 10.1016/j.jemermed.2017.06.029 [published Online First: 04 Oct 2017]
108. Van Der Meer D, H., Pranger AD, Jansen I, et al. Fatale intoxicatie met nicotine voor e-sigaret [Fatal intoxication with nicotine for e-cigarette]. *Ned Tijdschr Geneeskd* 2017;161(43):D1591.
109. Demir E, Topal S. Sudden sensorineural hearing loss associated with electronic cigarette liquid: The first case in the literature. *Int J Pediatr Otorhinolaryngol* 2018;114:26-28. doi: 10.1016/j.ijporl.2018.08.019
110. Paik JH, Kang S, Durey A, et al. Bradicardia sintomática causada por intoxicação por nicotina. *Rev Bras Ter Intensiva* 2018;30(1):121-26. doi: 10.5935/0103-507x.20180018
111. Noble MJ, Longstreet B, Hendrickson RG, et al. Unintentional pediatric ingestion of electronic cigarette nicotine refill liquid necessitating intubation. *Ann Emerg Med* 2017;69(1):94-97. doi: 10.1016/j.annemergmed.2016.08.448
112. Maridet C, Atge B, Amici JM, et al. The electronic cigarette: The new source of nickel contact allergy of the 21st century? *Contact Dermatitis* 2015;73(1):49-50. doi: 10.1111/cod.12373
113. Azevedo A, Lobo I, Selores M. Allergic contact dermatitis and electronic cigarettes: Is nickel to blame? *Contact Dermatitis* 2019;81:135-36. doi: 10.1111/cod.13257 [published Online First: 04 March 2019]
114. Ormerod E, Stone N. Contact allergy and electronic cigarettes (and eyelash curlers). *Clin Exp Dermatol* 2017;42(6):682-83. doi: 10.1111/ced.13138 [published Online First: 22 May 2017]
115. Hughes A, Hendrickson RG. Does vaping cause seizures? The need for comprehensive drug testing. *Clin Toxicol (Phila)* 2020;58(3):217-18. doi: 10.1080/15563650.2019.1618468
116. Berm EJJL, Ruijsbroek R, Loonen AJM, et al. Overstap op e-sigaret beïnvloedt medicijnconcentratie [Switching to e-cigarettes affects drug concentration]. *Ned Tijdschr Geneeskd* 2015;159:A9090.
117. Nonner TS, Timmer SJ. Sterke stijging van clozapinespiegel na overschakelen van traditionele op elektronische sigaretten [Clozapine and the electronic cigarette; a case study]. *Tijdschr Psychiatr* 2016;58(4):314-17.
118. Khorassani F, Kaufman M, Lopez lV. Supatherapeutic serum clozapine concentration after transition from traditional to electronic cigarettes. *J Clin Psychopharmacol* 2018;38(4):391-92. doi: 10.1097/JCP.0000000000000899
119. Kocar T, Freudenmann RW, Spitzer M, et al. Switching from tobacco smoking to electronic cigarettes and the impact on clozapine levels. *J Clin Psychopharmacol* 2018;38(5):528-29. doi: 10.1097/JCP.0000000000000948
120. Krishnan NM, Han KD, Nahabedian MY. Can e-cigarettes cause free flap failure? A case of arterial vasospasm induced by electronic cigarettes following microsurgical breast reconstruction. *Plast Reconstr Surg Glob Open* 2016;4(1):e596. doi: 10.1097/GOX.0000000000000576
121. Fracol M, Dorfman R, Janes L, et al. The surgical impact of e-cigarettes: A case report and review of the current literature. *Arch Plast Surg* 2017;44(6):477-81. doi: 10.5999/aps.2017.00087
122. Agochukwu N, Liau JY. Debunking the myth of e-cigarettes: A case of free flap compromise due to e-cigarette use within the first 24 hours. *J Plast Reconstr Aesthet Surg* 2018;71(3):451-53. doi: 10.1016/j.bjps.2017.09.017
123. Vannier S, Ronziere T, Ferre JC, et al. Reversible cerebral vasoconstriction syndrome triggered by an electronic cigarette: Case report. *Eur J Neurol* 2015;22(5):e64-65. doi: 10.1111/ene.12657
124. Camus M, Gallois C, Marteau P. Ulcerative colitis and electronic cigarette: What's the matter? *Am J Gastroenterol* 2014;109(4):608-09. doi: 10.1038/ajg.2013.439
125. Farsalinos KE, Romagna G. Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: A case report. *Clin Med Insights Case Rep* 2013a;6:15-21. doi: 10.4137/CCRep.S11175

126. Rasanen M, Helantera I, Kalliomaki J, et al. A case report of successful kidney donation after brain death following nicotine intoxication. *Transplant Proc* 2017;49(1):229-31. doi: 10.1016/j.transproceed.2016.08.043 [published Online First: 16 Jan 2017]
127. Lee J, You Y, Park JS, et al. Liver donation after brain death following intentional ingestion of 99% e-cigarette liquid nicotine 10 mL. *Exp Clin Transplant* 2018;1(1):1. doi: 10.6002/ect.2017.0275
128. Caponnetto P, Polosa R, Russo C, et al. Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep* 2011a;5:585. doi: 10.1186/1752-1947-5-585
129. Caponnetto P. Smoking cessation with e-cigarettes in smokers with a documented history of depression and recurring relapses. *Int J Clin Med* 2011b;2(3):281-84. doi: 10.4236/ijcm.2011.23046
130. Keith RJ, Fetterman JL, Orimoloye OA, et al. Characterization of volatile organic compound (VOC) metabolites in cigarette smokers, electronic nicotine device users, dual users and non-users of tobacco. *Nicotine Tob Res* 2019 doi: 10.1093/ntr/ntz021 [published Online First: 13 Feb 2019]
131. Nguyen H, Kitzmiller JP, Nguyen KT, et al. Oral carcinoma associated with chronic use of electronic cigarettes. *Otolaryngol (Sunnyvale)* 2017;07(2):304. doi: 10.4172/2161-119X.1000304 [published Online First: 26 Apr 2017]
132. Blagev DP, Harris D, Dunn AC, et al. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: A prospective observational cohort study. *Lancet* 2019;394(10214):2073-83. doi: 10.1016/S0140-6736(19)32679-0 [published Online First: 08 Nov 2019]
133. Bradford LE, Rebuli ME, Ring BJ, et al. Danger in the vapor? ECMO for adolescents with status asthmaticus after vaping. *J Asthma* 2019 doi: 10.1080/02770903.2019.1643361 [published Online First: 27 Jul 2019]
134. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. *N Engl J Med* 2019;381(18):1780-81. doi: 10.1056/NEJMc1913069 [published Online First: 31 Oct 2019]
135. Mukhopadhyay S, Mehrad M, Dammert P, et al. Lung biopsy findings in severe pulmonary illness associated with e-cigarette use (vaping). *Am J Clin Pathol* 2020;153(1):30-39. doi: 10.1093/ajcp/aqz182
136. Henry TS, Kanne JP, Kligerman SJ. Imaging of vaping-associated lung disease. *N Engl J Med* 2019;381:1486-87. doi: 10.1056/NEJMc1911995 [published Online First: 10 Oct 2019]
137. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): Case series and diagnostic approach. *Lancet Respir Med* 2019;7(12):1017-26. doi: 10.1016/S2213-2600(19)30415-1 [published Online First: 08 Nov 2019]
138. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin - Preliminary report. *N Engl J Med* 2020;382:903-16. doi: 10.1056/NEJMoa1911614
139. Triantafyllou GA, Tiberio PJ, Zou RH, et al. Vaping-associated acute lung injury: A case series. *Am J Respir Crit Care Med* 2019;200(11):1430-31. doi: 10.1164/rccm.201909-1809LE [published Online First: 01 Oct 2019]
140. Brownson EG, Thompson CM, Goldsberry S, et al. Explosion injuries from e-cigarettes. *N Engl J Med* 2016;375(14):1400-02. doi: 10.1056/NEJMc1608478
141. Herlin C, Bekara F, Bertheuil N, et al. Deep burns caused by electronic vaping devices explosion. *Burns* 2016;42(8):1875-77. doi: 10.1016/j.burns.2016.08.015
142. Kumetz EA, Hurst ND, Cudnik CJ, et al. Electronic cigarette explosion injuries. *Am J Emerg Med* 2016;34(11):2252.e1-52.e3. doi: 10.1016/j.ajem.2016.04.010
143. Nicoll KJ, Rose AM, Khan MAA, et al. Thigh burns from exploding e-cigarette lithium ion batteries: First case series. *Burns* 2016;42(4):e42-e46. doi: 10.1016/j.burns.2016.03.027
144. Sheckter C, Chattopadhyay A, Paro J, et al. Burns resulting from spontaneous combustion of electronic cigarettes: A case series. *Burns Trauma* 2016;4:35. doi: 10.1186/s41038-016-0061-9
145. Arnaout A, Khashaba H, Dobbs T, et al. The Southwest UK Burns Network (SWUK) experience of electronic cigarette explosions and review of literature. *Burns* 2017;43(4):e1-e6. doi: 10.1016/j.burns.2017.01.008
146. Jiwani AZ, Williams JF, Rizzo JA, et al. Thermal injury patterns associated with electronic cigarettes. *Int J Burns Trauma* 2017;7(1):1-5.
147. Patterson SB, Beckett AR, Lintner A, et al. A novel classification system for injuries after electronic cigarette explosions. *J Burn Care Res* 2017;38(1):e95-e100. doi: 10.1097/BCR.0000000000000471 [published Online First: 01 Jan 2017]
148. Ramirez JI, Ridgway CA, Lee JG, et al. The unrecognized epidemic of electronic cigarette burns. *J Burn Care Res* 2017;38(4):220-24. doi: 10.1097/BCR.0000000000000472
149. Smith SL, Smith C, Cheatham M. Electronic cigarettes: A burn case series. *J Nurse Pract* 2017;13(10):693-99. doi: 10.1016/j.nurpra.2017.09.003 [published Online First: 24 Oct 2017]
150. Harshman J, Vojvodic M, Rogers AD. Burns associated with e-cigarette batteries: A case series and literature review. *CJEM* 2018;20(S2):S20-S28. doi: 10.1017/cem.2017.32 [published Online First: 01 Jun 2017]
151. Gibson CJS, Eshraghi N, Kemalyan NA, et al. Electronic cigarette burns: A case series. *Trauma* 2019;21(2):103-06. doi: 10.1177/1460408617738812 [published Online First: 08 Jan 2018]

152. Kite AC, Le BQ, Cumpston KL, et al. Blast injuries caused by vape devices: 2 case reports. *Ann Plast Surg* 2016;77(6):620-22. doi: 10.1097/SAP.0000000000000875
153. Hickey S, Goverman J, Friedstat J, et al. Thermal injuries from exploding electronic cigarettes. *Burns* 2018;44(5):1294-301. doi: 10.1016/j.burns.2018.02.008
154. Maraqa T, Mohamed MAT, Salib M, et al. Too hot for your pocket! Burns from e-cigarette lithium battery explosions: A case series. *J Burn Care Res* 2018;39(6):1043-47. doi: 10.1093/jbcr/irx015 [published Online First: 04 Dec 2017]
155. Paley GL, Echalier E, Eck TW, et al. Corneoscleral laceration and ocular burns caused by electronic cigarette explosions. *Cornea* 2016;35(7):1015-18. doi: 10.1097/ICO.0000000000000881
156. Simpson LJ, Lye G. Burns injuries from e-cigarettes kept in pockets. *BMJ* 2019;364:l554. doi: 10.1136/bmj.l554 [published Online First: 07 Feb 2019]
157. Serror K, Chaouat M, Legrand MM, et al. Burns caused by electronic vaping devices (e-cigarettes): A new classification proposal based on mechanisms. *Burns* 2018;44(3):544-48. doi: 10.1016/j.burns.2017.09.005 [published Online First: 19 Oct 2017]
158. Treitl D, Solomon R, Davare DL, et al. Full and partial thickness burns from spontaneous combustion of e-cigarette lithium-ion batteries with review of literature. *J Emerg Med* 2017;53(1):121-25. doi: 10.1016/j.jemermed.2017.03.031 [published Online First: 10 May 2017]
159. Jalkanen V, Varela V, Kalliomaki J. Case report: Two severe cases of suicide attempts using nicotine containing e-cigarette liquid [Sähkötupakkanesteen itsetuhoinen käyttö]. *Duodecim* 2016;132(16):1480-83.
160. Sommerfeld K, Lukasik-Glebocka M, Kulza M, et al. Intravenous and oral suicidal e-liquid poisonings with confirmed nicotine and cotinine concentrations. *Forensic Sci Int* 2016;262:e15-20. doi: 10.1016/j.forsciint.2016.03.005
161. Park EJ, Min YG. The emerging method of suicide by electronic cigarette liquid: A case report. *J Korean Med Sci* 2018;33(11):e52. doi: 10.3346/jkms.2018.33.e52
162. Rojkiewicz M, Majchrzak M, Celinski R, et al. Identification and physicochemical characterization of 4-fluorobutyrfentanyl (1-((4-fluorophenyl)(1-phenethylpiperidin-4-yl)amino)butan-1-one, 4-FBF) in seized materials and post-mortem biological samples. *Drug Test Anal* 2017;9(3):405-14. doi: 10.1002/dta.2135
163. Maessen GC, Wijnhoven AM, Neijzen RL, et al. Nicotine intoxication by e-cigarette liquids: A study of case reports and pathophysiology. *Clin Toxicol (Phila)* 2019:1-8. doi: 10.1080/15563650.2019.1636994
164. Shim TN, Kosztyuova T. Allergic contact dermatitis to electronic cigarette. *Dermatitis* 2018;29(2):94-95. doi: 10.1097/DER.0000000000000337
165. Hswen Y, Brownstein JS. Real-time digital surveillance of vaping-induced pulmonary disease. *N Engl J Med* 2019;381:1778-80. doi: 10.1056/NEJMc1912818 [published Online First: 31 Oct 2019]
166. Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use-associated lung injury - 10 states, August-October 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(45):1040-41. doi: 10.15585/mmwr.mm6845e2
167. Dohnalek HM, Harley EH. Analysis of electronic cigarette-related injury presenting to U.S. emergency departments, 2008-2017. *J Emerg Med* 2019;57(3):399-404. doi: 10.1016/j.jemermed.2019.05.037
168. Wang B, Liu S, Persoskie A. Poisoning exposure cases involving e-cigarettes and e-liquid in the United States, 2010-2018. *Clin Toxicol (Phila)* 2019a;9:1-7. doi: 10.1080/15563650.2019.1661426
169. Durmowicz EL, Rudy SF, Chen IL. Electronic cigarettes: analysis of FDA adverse experience reports in non-users. *Tob Control* 2015;25(2):242. doi: 10.1136/tobaccocontrol-2015-052235
170. Vickerman KA, Carpenter KM, Altman T, et al. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res* 2013;15(10):1787-93. doi: 10.1093/ntr/ntt061
171. Davidson K, Brancato A, Heetderks P, et al. Outbreak of electronic-cigarette-associated acute lipoid pneumonia - North Carolina, July-August 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(36):784-86. doi: 10.15585/mmwr.mm6836e1 [published Online First: 13 Sep 2019]
172. Lewis N. E-cigarette use, or vaping, practices and characteristics among persons with associated lung injury — Utah, April–October 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(42):952-56. doi: 10.15585/mmwr.mm6842e1 [published Online First: 25 Oct 2019]
173. Kapaya M. Use of electronic vapor products before, during, and after pregnancy among women with a recent live birth — Oklahoma and Texas, 2015. *MMWR Morb Mortal Wkly Rep* 2019;68(8):189-94. doi: 10.15585/mmwr.mm6808a1 [published Online First: 01 Mar 2019]
174. Corey CG, Chang JT, Rostron BL. Electronic nicotine delivery system (ENDS) battery-related burns presenting to US emergency departments, 2016. *Inj Epidemiol* 2018;5:4. doi: 10.1186/s40621-018-0135-1
175. Rudy SF, Durmowicz EL. Electronic nicotine delivery systems: overheating, fires and explosions. *Tob Control* 2016;26:10-18. doi: 10.1136/tobaccocontrol-2015-052626
176. Rossheim ME, Livingston MD, Soule EK, et al. Electronic cigarette explosion and burn injuries, US emergency departments 2015-2017. *Tob Control* 2018;28:472-74. doi: 10.1136/tobaccocontrol-2018-054518 [published Online First: 20 Jun 2019]

177. Choi A, Le M, Rahim T, et al. Electronic cigarette exposures reported to the British Columbia Drug and Poison Information Centre: An observational case series. *CMAJ open* 2019;7(3):E462-E71. doi: 10.9778/cmajo.20180203
178. Richmond SA, Pike I, Maguire JL, et al. E-cigarettes: A new hazard for children and adolescents. *Paediatr Child Health* 2018;23(4):255-59. doi: 10.1093/pch/pxx204 [published Online First: 01 Mar 2018]
179. De La Oliva U, Moenor JLC. Exposures to electronic cigarettes: Calls to the poison center in Spain [Exposiciones a cigarrillos electrónicos: Consultas telefónicas al centro antitóxico en España]. *Revista Espanola de Medicina Legal* 2014;40(4):146-49. doi: 10.1016/j.reml.2014.06.003
180. Ang E, Tuthill D, Thompson J. E-cigarette liquid ingestion: A fast growing accidental issue in children. *Arch Dis Child* 2018;103(11):1091. doi: 10.1136/archdischild-2018-314886 [published Online First: 18 Oct 2018]
181. Vardavas CI, Girvalaki C, Filippidis FT, et al. Characteristics and outcomes of e-cigarette exposure incidents reported to 10 European poison centers: A retrospective data analysis. *Tob Induc Dis* 2017;15(August):36. doi: 10.1186/s12971-017-0141-z
182. Chatham-Stephens K, Law R, Taylor E, et al. Notes from the field: Calls to poison centers for exposures to electronic cigarettes-United States, September 2010-February 2014. *MMWR Morb Mortal Wkly Rep* 2014;63(13):292-93.
183. Vakkalanka JP, Hardison Jr. LS, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. poison centers. *Clin Toxicol (Phila)* 2014;52(5):542-48. doi: 10.3109/15563650.2014.913176
184. Chatham-Stephens K, Law R, Taylor E, et al. Exposure calls to U. S. poison centers involving electronic cigarettes and conventional cigarettes-September 2010-December 2014. *J Med Toxicol* 2016;12:350-57. doi: 10.1007/s13181-016-0563-7
185. Kamboj A, Spiller HA, Casavant MJ, et al. Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. *Pediatrics* 2016;137(6):e20160041. doi: 10.1542/peds.2016-0041
186. Wang B, Rostron B. Tobacco-related poison events involving young children in the US, 2001-2016. *Tob Regul Sci* 2017;3(4):525-35. doi: 10.18001/TRS.3.4.12
187. Govindarajan P, Spiller HA, Casavant MJ, et al. E-cigarette and liquid nicotine exposures among young children. *Pediatrics* 2018;141(5):e20173361. doi: 10.1542/peds.2017-3361
188. Cantrell FL. Adverse effects of e-cigarette exposures. *J Community Health* 2014a;39(3):614-16. doi: 10.1007/s10900-013-9807-5
189. Cantrell FL, Clark RF. More on nicotine poisoning in infants. *N Engl J Med* 2014b;371(9):880. doi: 10.1056/NEJMc1407921
190. Forrester MB. Pediatric exposures to electronic cigarettes reported to Texas poison centers. *J Emerg Med* 2015;49(2):136-42. doi: 10.1016/j.jemermed.2014.12.073
191. LoVecchio F, Zoph O. Incidence of electronic cigarette exposures in children skyrockets in Arizona. *Am J Emerg Med* 2015;33(6):834-35. doi: 10.1016/j.ajem.2015.02.036
192. Ordonez JE, Kleinschmidt KC, Forrester MB. Electronic cigarette exposures reported to Texas poison centers. *Nicotine Tob Res* 2015;17(2):209-11. doi: 10.1093/ntr/ntu223
193. Valentine N, McClelland E, Bryant J, et al. Electronic cigarettes in Mississippi: Issues facing healthcare providers and policy makers. *J Miss State Med Assoc* 2016a;57(6):181-89.
194. Weiss D, Tomasallo CD, Meiman JG, et al. Electronic cigarette exposure: calls to Wisconsin poison control centers, 2010-2015. *WMJ* 2016;115(6):306-10.
195. Hughes A, Hendrickson RG. An epidemiologic and clinical description of e-cigarette toxicity. *Clin Toxicol (Phila)* 2019b;57(4):287-93. doi: 10.1080/15563650.2018.1510503 [published Online First: 11 Oct 2018]
196. Bronstein AC, Spyker DA, Cantilena LR, et al. 2010 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th annual report. *Clin Toxicol (Phila)* 2011;49(10):910-41. doi: 10.3109/15563650.2011.635149
197. Chang JT, Rostron BL. Electronic nicotine delivery system (ENDS) liquid nicotine exposure in young children presenting to US emergency departments, 2018. *Inj Epidemiol* 2019a;6:43. doi: 10.1186/s40621-019-0219-6
198. Chang JT, Wang B, Chang CM, et al. National estimates of poisoning events related to liquid nicotine in young children treated in US hospital emergency departments, 2013-2017. *Inj Epidemiol* 2019b;6:10. doi: 10.1186/s40621-019-0188-9
199. Motooka Y, Matsui T, Slaton RM, et al. Adverse events of smoking cessation treatments (nicotine replacement therapy and non-nicotine prescription medication) and electronic cigarettes in the Food and Drug Administration Adverse Event Reporting System, 2004-2016. *SAGE Open Med* 2018 doi: 10.1177/2050312118777953 [published Online First: 21 May 2018]
200. Baweja R, Curci KM, Yingst J, et al. Views of experienced electronic cigarette users. *Addict Res Theory* 2016;24(1):80-88. doi: 10.3109/16066359.2015.1077947

201. Farsalinos KE, Romagna G, Tsiapras D, et al. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health* 2014c;11(4):4356-73. doi: 10.3390/ijerph110404356
202. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst Abuse* 2013b;7:139-46. doi: 10.4137/SART.S12756
203. Etter J, Eissenberg T. Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. *Drug Alcohol Depend* 2015;147:68-75. doi: 10.1016/j.drugalcdep.2014.12.007
204. Piper ME, Baker TB, Benowitz NL, et al. Dual users compared to smokers: Demographics, dependence, and biomarkers. *Nicotine Tob Res* 2018;21(9):1279-84. doi: 10.1093/ntr/nty231 [published Online First: 26 Oct 2018]
205. Comiford AL, Rhoades DA, Spicer P, et al. E-cigarettes and tobacco exposure biomarkers among American Indian smokers. *Am J Health Behav* 2018;42(6):101-09. doi: 10.5993/AJHB.42.6.10
206. Johnson JM, Muilenburg JL, Rathbun SL, et al. Elevated nicotine dependence scores among electronic cigarette users at an electronic cigarette convention. *J Community Health* 2018;43(1):164-74. doi: 10.1007/s10900-017-0399-3
207. Boykan R, Goniewicz ML, Messina CR. Evidence of nicotine dependence in adolescents who use Juul and similar pod devices. *Int J Environ Res Public Health* 2019;16(12):17. doi: 10.3390/ijerph16122135 [published Online First: 17 June 2019]
208. Jankowski M, Krzystanek M, Zejda JE, et al. E-cigarettes are more addictive than traditional cigarettes-A study in highly educated young people. *Int J Environ Res Public Health* 2019;16(13):2279. doi: 10.3390/ijerph16132279 [published Online First: 27 Jun 2019]
209. Bianco CL. Rates of electronic cigarette use among adults with a chronic mental illness. *Addict Behav* 2019;89:1-4. doi: 10.1016/j.addbeh.2018.08.033
210. Chadi N, Li G, Cerda N, et al. Depressive symptoms and suicidality in adolescents using e-cigarettes and marijuana: A secondary data analysis from the Youth Risk Behavior Survey. *J Addict Med* 2019;13(5):362-65. doi: 10.1097/ADM.0000000000000506
211. Bandiera FC, Loukas A, Wilkinson AV, et al. Associations between tobacco and nicotine product use and depressive symptoms among college students in Texas. *Addict Behav* 2016;63:19-22. doi: 10.1016/j.addbeh.2016.06.024
212. Kim JS, Kim K. Electronic cigarette use and suicidal behaviors among adolescents. *J Public Health (Oxf)* 2019:fdz086. doi: 10.1093/pubmed/fdz086 [published Online First: 23 Jul 2019]
213. Lee Y, Lee K-S. Association of depression and suicidality with electronic and conventional cigarette use in South Korean adolescents. *Subst Use Misuse* 2019a;54(6):934-43. doi: 10.1080/10826084.2018.1552301 [published Online First: 14 Jan 2019]
214. Zvolensky MJ, Garey L, Mayorga NA, et al. Pain severity and anxiety sensitivity interplay among exclusive and dual electronic cigarette users. *J Stud Alcohol Drugs* 2019;80(2):211-19. doi: 10.15288/jsad.2019.80.211
215. Lanza HI, Pittman P, Batshoun J. Obesity and cigarette smoking: Extending the link to e-cigarette/vaping use. *Am J Health Behav* 2017;41(3):338-47. doi: 10.5993/AJHB.41.3.13
216. Morean ME, Bold KW, Kong G, et al. High school students' use of flavored e-cigarette e-liquids for appetite control and weight loss. *Addict Behav* 2019;102:106139. doi: 10.1016/j.addbeh.2019.106139
217. Boddu SA, Bojanowski CM, Lam MT, et al. Use of e-cigarettes with conventional tobacco is associated with decreased sleep quality in women. *Am J Respir Crit Care Med* 2019;200(11):1431-34. doi: 10.1164/rccm.201904-0890LE
218. Brett EI, Miller MB, Leavens ELS, et al. Electronic cigarette use and sleep health in young adults. *J Sleep Res* 2019;-:e12902. doi: 10.1111/jsr.12902 [published Online First: 04 Sept 2019]
219. Riehm KE, Rojo-Wissar DM, Feder KA, et al. E-cigarette use and sleep-related complaints among youth. *J Adolesc* 2019;76:48-54. doi: 10.1016/j.adolescence.2019.08.009
220. Lequy E, Wiernik E, Cyr D, et al. Poor perceived health is associated with current use of electronic cigarette among current and former smokers: Findings from the CONSTANCES cohort. *Eur Addict Res* 2019;25(6):310-19. doi: 10.1159/000502517
221. Boas Z, Gupta P, Moheimani RS, et al. Activation of the "Splenocardiac Axis" by electronic and tobacco cigarettes in otherwise healthy young adults. *Physiol Rep* 2017;5(17):pii: e13393. doi: 10.14814/phy2.13393
222. Alzahrani T, Pena I, Temesgen N, et al. Association between electronic cigarette use and myocardial infarction. *Am J Prev Med* 2018;55(4):455-61. doi: 10.1016/j.amepre.2018.05.004
223. Farsalinos KE, Polosa R, Cibella F, et al. Is e-cigarette use associated with coronary heart disease and myocardial infarction? Insights from the 2016 and 2017 National Health Interview Surveys. *Ther Adv Chronic Dis* 2019;10:1-10. doi: 10.1177/2040622319877741

224. Wang JB, Olgin JE, Nah G, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One* 2018;13(7):e0198681. doi: 10.1371/journal.pone.0198681 [published Online First: 25 Jul 2018]
225. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between e-cigarette use and cardiovascular disease among never and current combustible cigarette smokers: BRFSS 2016 & 2017. *Am J Med* 2019a;132(8):949-54.e2. doi: 10.1016/j.amjmed.2019.02.016
226. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study. *Ann Intern Med* 2017;166(6):390-400. doi: 10.7326/M16-1107
227. Chaffee BW, Jacob P, Couch ET, et al. Exposure to a tobacco-specific carcinogen among adolescent smokeless tobacco users in rural California, United States. *Nicotine Tob Res* 2019 doi: 10.1093/ntr/ntz147 [published Online First: 23 Aug 2019]
228. Franco T, Trapasso S, Puzzo L, et al. Electronic cigarette: Role in the primary prevention of oral cavity cancer. *Clin Med Insights Ear Nose Throat* 2016;9:7-12. doi: 10.4137/CMENT.S40364
229. Bustamante G, Ma B, Yakovlev G, et al. Presence of the carcinogen N'-nitrosonornicotine in saliva of e-cigarette users. *Chem Res Toxicol* 2018;31(8):731-38. doi: 10.1021/acs.chemrestox.8b00089 [published Online First: 18 July 2018]
230. Carroll DM, Wagener TL, Stephens LD, et al. The relationship between nicotine metabolism and nicotine and carcinogen exposure among American Indian commercial cigarette smokers and electronic nicotine delivery system users. *Addict Behav* 2018;92:58-63. doi: 10.1016/j.addbeh.2018.10.038
231. Reidel B, Radicioni G, Clapp PW, et al. E-cigarette use causes a unique innate immune response in the lung, involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med* 2018;197(4):492-501. doi: 10.1164/rccm.201708-1590OC
232. Meo SA, Ansary MA, Barayan FR, et al. Electronic cigarettes: Impact on lung function and fractional exhaled nitric oxide among healthy adults. *Am J Mens Health* 2019;13(1):1557988318806073. doi: 10.1177/1557988318806073
233. Wang MP, Ho SY, Leung LT, et al. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. *JAMA Pediatr* 2016;170(1):89-91. doi: 10.1001/jamapediatrics.2015.3024
234. Hedman L, Backman H, Stridsman C, et al. Association of electronic cigarette use with smoking habits, demographic factors, and respiratory symptoms. *JAMA Netw Open* 2018;1(3):e180789. doi: 10.1001/jamanetworkopen.2018.0789
235. Lestari KS, Humairo MV, Agustina U. Formaldehyde vapor concentration in electronic cigarettes and health complaints of electronic cigarettes smokers in Indonesia. *J Environ Public Health* 2018;2018:9013430. doi: 10.1155/2018/9013430 [published Online First: 11 Jul 2018]
236. King JL, Reboussin BA, Wiseman KD, et al. Adverse symptoms users attribute to e-cigarettes: Results from a national survey of US adults. *Drug Alcohol Depend* 2019;196:9-13. doi: 10.1016/j.drugalcdep.2018.11.030
237. Li D, Sundar IK, McIntosh S, et al. Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: cross-sectional results from the Population Assessment of Tobacco and Health (PATH) study, wave 2. *Tob Control* 2019 doi: 10.1136/tobaccocontrol-2018-054694 [published Online First: 13 Feb 2019]
238. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic cigarette use and respiratory symptoms in adolescents. *Am J Respir Crit Care Med* 2017;195(8):1043-49. doi: 10.1164/rccm.201604-0804OC
239. Schweitzer RJ, Wills TA, Tam E, et al. E-cigarette use and asthma in a multiethnic sample of adolescents. *Prev Med* 2017;105:226-31. doi: 10.1016/j.ypmed.2017.09.023 [published Online First: 28 Sep 2017]
240. Choi K, Bernat D. E-cigarette use among Florida youth with and without asthma. *Am J Prev Med* 2016;51(4):446-53. doi: 10.1016/j.amepre.2016.03.010
241. Cho JH, Paik SY. Association between electronic cigarette use and asthma among high school students in South Korea. *PLoS One* 2016;11(3):e0151022. doi: 10.1371/journal.pone.0151022
242. Kim SY, Sim S, Choi HG. Active, passive, and electronic cigarette smoking is associated with asthma in adolescents. *Sci Rep* 2017;7:17789. doi: 10.1038/s41598-017-17958-y [published Online First: 19 Dec 2017]
243. AboElNaga HH. Electronic cigarettes: Not an advantageous alternative to conventional smoking in asthma. *Egypt J Chest Dis Tuberc* 2018;67(4):427-32. doi: 10.4103/ejcdt.ejcdt_83_18
244. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. *BMC Pulm Med* 2019b;19:180. doi: 10.1186/s12890-019-0950-3 [published Online First: 16 Oct 2019]
245. Perez MF, Atuegwu NC, Oncken C, et al. Association between electronic cigarette use and asthma in never-smokers. *Ann Am Thorac Soc* 2019;16(11):1453-56. doi: 10.1513/AnnalsATS.201904-338RL [published Online First: 01 Nov 2019]

246. Wills TA, Pagano I, Williams RJ, et al. E-cigarette use and respiratory disorder in an adult sample. *Drug Alcohol Depend* 2019;194:363-70. doi: 10.1016/j.drugalcdep.2018.10.004
247. Ghinai I, Pray IW, Navon L, et al. E-cigarette product use, or vaping, among persons with associated lung injury - Illinois and Wisconsin, April-September 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(39):865-69. doi: 10.15585/mmwr.mm6839e2 [published Online First: 04 Oct 2019]
248. Martin EM, Clapp PW, Rebuli ME, et al. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *Am J Physiol Lung Cell Mol Physiol* 2016;311(1):L135-44. doi: 10.1152/ajplung.00170.2016
249. Bayly JE, Bernat D, Porter L, et al. Secondhand exposure to aerosols from electronic nicotine delivery systems and asthma exacerbations among youth with asthma. *Chest* 2019;155(1):88-93. doi: 10.1016/j.chest.2018.10.005
250. Tuhanioglu B, Erkan SO, Ozdas T, et al. The effect of electronic cigarettes on voice quality. *J Voice* 2018;33(5):811.e13-11.e17. doi: 10.1016/j.jvoice.2018.03.015 [published Online First: 05 Jun 2018]
251. Tackett AP, Leavens ELS, Wiedenmann A, et al. Preliminary exploration of secondhand smoke exposure in youth with sickle cell disease: biochemical verification, pulmonary functioning, and health care utilization. *Psychol Health Med* 2019;24(1):35-42. doi: 10.1080/13548506.2018.1516294 [published Online First: 11 Sep 2018]
252. Cho JH. The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: A cross-sectional study. *PLoS One* 2017;12(7):e0180506. doi: 10.1371/journal.pone.0180506
253. Javed F, Abduljabbar T, Vohra F, et al. Comparison of periodontal parameters and self-perceived oral symptoms among cigarette smokers, individuals vaping electronic cigarettes, and never-smokers. *J Periodontol* 2017;88(10):1059-65. doi: 10.1902/jop.2017.170197 [published Online First: 01 Oct 2017]
254. Akinkugbe AA. Cigarettes, e-cigarettes, and adolescents' oral health: findings from the Population Assessment of Tobacco and Health (PATH) Study. *JDR Clin Trans Res* 2018;4(3):276-83. doi: 10.1177/2380084418806870
255. Al-Aali KA, Alrabiah M, ArRejaie AS, et al. Peri-implant parameters, tumor necrosis factor-alpha, and interleukin-1 beta levels in vaping individuals. *Clin Implant Dent Relat Res* 2018;20(3):410-15. doi: 10.1111/cid.12597
256. AlQahtani MA, Alayad AS, Alshihri A, et al. Clinical peri-implant parameters and inflammatory cytokine profile among smokers of cigarette, e-cigarette, and waterpipe. *Clin Implant Dent Relat Res* 2018;20(6):1016-21. doi: 10.1111/cid.12664 [published Online First: 12 Sept 2018]
257. Jeong W, Choi D-W, Kim YK, et al. Associations of electronic and conventional cigarette use with periodontal disease in South Korean adults. *J Periodontol* 2020;91(1):55-64. doi: 10.1002/JPER.19-0060
258. Vora MV, Chaffee BW. Tobacco-use patterns and self-reported oral health outcomes: A cross-sectional assessment of the Population Assessment of Tobacco and Health study, 2013-2014. *J Am Dent Assoc* 2019;150(5):332-44.e2. doi: 10.1016/j.adaj.2018.12.004
259. Huilgol P, Bhatt SP, Biligowda N, et al. Association of e-cigarette use with oral health: A population-based cross-sectional questionnaire study. *J Public Health (Oxf)* 2019;41(2):354-61. doi: 10.1093/pubmed/fdy082 [published Online First: 18 May 2018]
260. Mokeem SA, Alasqah MN, Michelogiannakis D, et al. Clinical and radiographic periodontal status and whole salivary cotinine, IL-1beta and IL-6 levels in cigarette- and waterpipe-smokers and e-cig users. *Environ Toxicol Pharmacol* 2018;61:38-43. doi: 10.1016/j.etap.2018.05.016 [published Online First: 23 May 2018]
261. ArRejaie AS, Al-Aali KA, Alrabiah M, et al. Proinflammatory cytokine levels and peri-implant parameters among cigarette smokers, individuals vaping electronic cigarettes, and non-smokers. *J Periodontol* 2019;90(4):367-74. doi: 10.1002/JPER.18-0045
262. Cichonska D, Kusiak A, Kochanska B, et al. Influence of electronic cigarettes on selected antibacterial properties of saliva. *Int J Environ Res Public Health* 2019;16(22):4433. doi: 10.3390/ijerph16224433
263. Mokeem SA, Abduljabbar T, Al-Kheraif AA, et al. Oral Candida carriage among cigarette- and waterpipe-smokers, and electronic cigarette users. *Oral Dis* 2019;25(1):319-26. doi: 10.1111/odi.12902 [published Online First: 25 May 2018]
264. Stewart CJ, Auchtung TA, Ajami NJ, et al. Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study. *PeerJ* 2018;6:e4693. doi: 10.7717/peerj.4693 [published Online First: 30 Apr 2018]
265. Alqahtani F, Alqahtani M, Albaqawi AH, et al. Comparison of cotinine levels in the peri-implant sulcular fluid among cigarette and waterpipe smokers, electronic-cigarette users, and nonsmokers. *Clin Implant Dent Relat Res* 2019;21(4):702-07. doi: 10.1111/cid.12813 [published Online First: 02 Jul 2019]
266. Badea M, Luzardo OP, Gonzalez-Antuna A, et al. Body burden of toxic metals and rare earth elements in non-smokers, cigarette smokers and electronic cigarette users. *Environ Res* 2018;166:269-75. doi: 10.1016/j.envres.2018.06.007 [published Online First: 13 Jun 2018]

267. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob Res* 2015;17(6):704-09. doi: 10.1093/ntr/ntu218
268. Goniewicz ML, Smith DM, Edwards KC, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Netw Open* 2018;1(8):e185937. doi: 10.1001/jamanetworkopen.2018.5937
269. Prokopowicz A, Sobczak A, Szula-Chraplewska M, et al. Exposure to cadmium and lead in cigarette smokers who switched to electronic cigarettes. *Nicotine Tob Res* 2018;21(9):1198-205. doi: 10.1093/ntr/nty161 [published Online First: 09 Aug 2018]
270. Jain RB. Concentrations of cadmium, lead, and mercury in blood among US cigarettes, cigars, electronic cigarettes, and dual cigarette-e-cigarette users. *Environ Pollut* 2019;251:970-74. doi: 10.1016/j.envpol.2019.05.041 [published Online First: 13 May 2019]
271. Rubinstein ML, Delucchi K, Benowitz NL, et al. Adolescent exposure to toxic volatile organic chemicals from e-cigarettes. *Pediatrics* 2018;141(4):e20173557. doi: 10.1542/peds.2017-3557
272. Aherrera A, Olmedo P, Grau-Perez M, et al. The association of e-cigarette use with exposure to nickel and chromium: A preliminary study of non-invasive biomarkers. *Environ Res* 2017;159:313-20. doi: 10.1016/j.envres.2017.08.014
273. Wei B, Goniewicz ML, O'Connor RJ, et al. Urinary metabolite levels of flame retardants in electronic cigarette users: A study using the data from NHANES 2013-2014. *Int J Environ Res Public Health* 2018;15(2):201. doi: 10.3390/ijerph15020201 [published Online First: 25 Jan 2018]
274. Wang Y, Wong L-Y, Meng L, et al. Urinary concentrations of monohydroxylated polycyclic aromatic hydrocarbons in adults from the U.S. Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013-2014). *Environ Int* 2019b;123:201-08. doi: 10.1016/j.envint.2018.11.068
275. Choi D-W, Jeon J, Lee SA, et al. Association between smoking behavior patterns and glycated hemoglobin levels in a general population. *Int J Environ Res Public Health* 2018;15(10):2260. doi: 10.3390/ijerph15102260
276. Atuegwu NC, Perez MF, Oncken C, et al. E-cigarette use is associated with a self-reported diagnosis of prediabetes in never cigarette smokers: Results from the behavioral risk factor surveillance system survey. *Drug Alcohol Depend* 2019a;205:107692. doi: 10.1016/j.drugalcdep.2019.107692 [published Online First: 28 Oct 2019]
277. Md Isa NM, Koh PY, Doraj P. The tear function in electronic cigarette smokers. *Optom Vis Sci* 2019;96(9):678-85. doi: 10.1097/OPX.0000000000001422
278. Ballbè M, Martínez-Sánchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environ Res* 2014;135:76-80. doi: 10.1016/j.envres.2014.09.005
279. Northrup TF, Stotts AL, Suchting R, et al. Medical staff contributions to thirdhand smoke contamination in a neonatal intensive care unit. *Tob Induc Dis* 2019;17(April):37. doi: 10.18332/tid/106116 [published Online First: 24 Apr 2019]
280. Yao T, Max W, Sung H-Y, et al. Relationship between spending on electronic cigarettes, 30-day use, and disease symptoms among current adult cigarette smokers in the U.S. *PLoS One* 2017;12(11):e0187399. doi: 10.1371/journal.pone.0187399 [published Online First: 07 Nov 2017]
281. Abafalvi L, Penzes M, Urban R, et al. Perceived health effects of vaping among Hungarian adult e-cigarette-only and dual users: a cross-sectional internet survey. *BMC Public Health* 2019;19(1):302. doi: 10.1186/s12889-019-6629-0
282. Mantey DS, Harrell MB, Case K, et al. Subjective experiences at first use of cigarette, e-cigarettes, hookah, and cigar products among Texas adolescents. *Drug Alcohol Depend* 2017;173:10-16. doi: 10.1016/j.drugalcdep.2016.12.010
283. Chen MS, Hall MG, Parada H, et al. Symptoms during adolescents' first use of cigarettes and e-cigarettes: A pilot study. *Int J Environ Res Public Health* 2017;14(10):1260. doi: 10.3390/ijerph14101260
284. Kyriakos C, Filippidis FT, Hitchman S, et al. Characteristics and correlates of electronic cigarette product attributes and undesirable events during e-cigarette use in six countries of the EUREST-PLUS ITC Europe Surveys. *Tob Induc Dis* 2018;16(2):A1. doi: 10.18332/tid/93545
285. Chang YC, Lee YH, Liu CT, et al. Patterns of e-cigarette use and self-reported health outcomes among smokers and non-smokers in the United States: A preliminary assessment. *J Subst Use* 2019c;24(1):79-87. doi: 10.1080/14659891.2018.1510053
286. Fuller TW, Acharya AP, Meyyappan T, et al. Comparison of bladder carcinogens in the urine of e-cigarette users versus non e-cigarette using controls. *Sci Rep* 2018;8:507. doi: 10.1038/s41598-017-19030-1 [published Online First: 11 Jan 2018]
287. Navon L, Jones CM, Ghinai I, et al. Risk factors for e-cigarette, or vaping, product use-associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products - Illinois, July-October 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(45):1034-39. doi: 10.15585/mmwr.mm6845e1

288. McDonnell BP, Dicker P, Regan CL. Electronic cigarettes and obstetric outcomes: a prospective observational study. *BJOG* 2020;127(6):750-56. doi: 10.1111/1471-0528.16110
289. Manzoli L, Flacco ME, Ferrante M, et al. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. *Tob Control* 2017;26(3):284-92. doi: 10.1136/tobaccocontrol-2015-052822
290. McMillen R, Klein JD, Wilson K, et al. E-cigarette use and future cigarette initiation among never smokers and relapse among former smokers in the PATH study. *Public Health Rep* 2019;134(5):528-36. doi: 10.1177/0033354919864369 [published Online First: 16 Aug 2019]
291. Du P, Fan T, Yingst J, et al. Changes in e-cigarette use behaviors and dependence in long-term e-cigarette users. *Am J Prev Med* 2019;57(3):374-83. doi: 10.1016/j.amepre.2019.04.021
292. Caponnetto P, Auditore R, Russo C, et al. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health* 2013;10(2):446-61. doi: 10.3390/ijerph10020446
293. Soar K, Kimber C, McRobbie H, et al. Nicotine absorption from e-cigarettes over 12 months. *Addict Behav* 2019;91:102-05. doi: 10.1016/j.addbeh.2018.07.019
294. Bandiera FC, Loukas A, Li X, et al. Depressive symptoms predict current e-cigarette use among college students in Texas. *Nicotine Tob Res* 2017;19(9):1102-06. doi: 10.1093/ntr/ntx014
295. Lechner WV, Janssen T, Kahler CW, et al. Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents. *Prev Med* 2017;96:73-78. doi: 10.1016/j.ypmed.2016.12.034 [published Online First: 23 Dec 2016]
296. Wiernik E, Airagnes G, Lequy E, et al. Electronic cigarette use is associated with depressive symptoms among smokers and former smokers: Cross-sectional and longitudinal findings from the Constances cohort. *Addict Behav* 2019;90:85-91. doi: 10.1016/j.addbeh.2018.10.021
297. Russo C, Cibella F, Mondati E, et al. Lack of substantial post-cessation weight increase in electronic cigarettes users. *Int J Environ Res Public Health* 2018;15(4):581. doi: 10.3390/ijerph15040581 [published Online First: 23 Mar 2018]
298. Marsden DG, Loukas A, Chen B, et al. Associations between frequency of cigarette and alternative tobacco product use and depressive symptoms: A longitudinal study of young adults. *Addict Behav* 2019;99:106078. doi: 10.1016/j.addbeh.2019.106078
299. Polosa R, Morjaria JB, Caponnetto P, et al. Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes. *Int J Environ Res Public Health* 2016a;13(11):1123. doi: 10.3390/ijerph13111123
300. Polosa R, Cibella F, Caponnetto P, et al. Health impact of e-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. *Sci Rep* 2017;7:13825. doi: 10.1038/s41598-017-14043-2 [published Online First: 17 Nov 2017]
301. Michaels BM, Craft P, Michaels JA, et al. Is nicotine replacement a safe alternative to smoking in plastic surgery patients? *Plast Reconstr Surg Glob Open* 2018;6(12):e2017. doi: 10.1097/GOX.0000000000002017 [published Online First: Dec 2018]
302. Polosa R, Morjaria J, Caponnetto P, et al. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int J Environ Res Public Health* 2014a;11(5):4965-77. doi: 10.3390/ijerph110504965
303. Polosa R, Morjaria JB, Caponnetto P, et al. Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov Med* 2016b;21(114):99-108.
304. Polosa R, Morjaria JB, Caponnetto P, et al. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir Res* 2016c;17:166. doi: 10.1186/s12931-016-0481-x
305. Bowler RP, Hansel NN, Jacobson S, et al. Electronic cigarette use in US adults at risk for or with COPD: Analysis from two observational cohorts. *J Gen Intern Med* 2017;32(12):1315-22. doi: 10.1007/s11606-017-4150-7
306. Flacco ME, Ferrante M, Fiore M, et al. Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. *Eur Rev Med Pharmacol Sci* 2019;23(1):402-12. doi: 10.26355/eurrev_201901_16789
307. Tatullo M, Gentile S, Paduano F, et al. Crosstalk between oral and general health status in e-smokers. *Medicine (Baltimore)* 2016;95(49):e5589. doi: 10.1097/MD.0000000000005589
308. ALHarthi SS, BinShabaib M, Akram Z, et al. Impact of cigarette smoking and vaping on the outcome of full-mouth ultrasonic scaling among patients with gingival inflammation: a prospective study. *Clin Oral Investig* 2018;23(6):2751-58. doi: 10.1007/s00784-018-2725-2
309. Atuegwu NC, Perez MF, Oncken C, et al. Association between regular electronic nicotine product use and self-reported periodontal disease status: Population Assessment of Tobacco and Health Survey. *Int J Environ Res Public Health* 2019b;16(7):pii: E1263. doi: 10.3390/ijerph16071263

310. Cardenas VM, Cen R, Clemens MM, et al. Use of electronic nicotine delivery systems (ENDS) by pregnant women I: Risk of small-for-gestational-age birth. *Tob Induc Dis* 2019;17(May):44. doi: 10.18332/tid/106089
311. Vansickel AR, Cobb CO, Weaver MF, et al. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": Nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;19(8):1945-53. doi: 10.1158/1055-9965.EPI-10-0288
312. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* 2012;107(8):1493-500. doi: 10.1111/j.1360-0443.2012.03791.x
313. Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacology (Berl)* 2013;227(3):377-84. doi: 10.1007/s00213-013-2983-2
314. Adriaens K, Van Gucht D, Declerck P, et al. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *Int J Environ Res Public Health* 2014;11(11):11220-48. doi: 10.3390/ijerph111111220
315. Nides MA, Leischow SJ, Bhatter M, et al. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav* 2014;38(2):265-74. doi: 10.5993/AJHB.38.2.12
316. Polosa R, Morjaria JB, Caponnetto P, et al. Effectiveness and tolerability of electronic cigarette in real-life: A 24-month prospective observational study. *Intern Emerg Med* 2014b;9(5):537-46. doi: 10.1007/s11739-013-0977-z
317. Caponnetto P, Maglia M, Cannella MC, et al. Impact of different e-cigarette generation and models on cognitive performances, craving and gesture: A randomized cross-over trial (CogEcig). *Front Psychol* 2017;8:127. doi: 10.3389/fpsyg.2017.00127
318. O'Connell G, Pritchard JD, Prue C, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med* 2019;14(6):853-61. doi: 10.1007/s11739-019-02025-3
319. Polosa R, Caponnetto P, Maglia M, et al. Success rates with nicotine personal vaporizers: A prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health* 2014c;14:1159. doi: 10.1186/1471-2458-14-1159
320. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010;19(1):87-88. doi: 10.1136/tc.2009.033498
321. De La Garza R, Shuman SL, Yammine L, et al. A pilot study of e-cigarette naive cigarette smokers and the effects on craving after acute exposure to e-cigarettes in the laboratory. *Am J Addict* 2019;28(5):361-66. doi: 10.1111/ajad.12895
322. St Helen G, Nardone N, Addo N, et al. Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users. *Addiction* 2019;115(4): 757-67. doi: 10.1111/add.14884
323. Dawkins L, Turner J, Hasna S, et al. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict Behav* 2012;37(8):970-73. doi: 10.1016/j.addbeh.2012.03.004
324. Hughes JR, Peters EN, Callas PW, et al. Withdrawal symptoms from e-cigarette abstinence among former smokers: A pre-post clinical trial. *Nicotine Tob Res* 2019a;22(5):734–39. doi: 10.1093/ntr/ntz129
325. Maloney SF, Breland A, Soule EK, et al. Abuse liability assessment of an electronic cigarette in combustible cigarette smokers. *Exp Clin Psychopharmacol* 2019;27(5):443–54. doi: 10.1037/pha0000261
326. Baldassarri SR, Hillmer AT, Anderson JM, et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: evidence from a PET imaging study. *Nicotine Tob Res* 2018;20(4):425-33. doi: 10.1093/ntr/ntx091 [published Online First: 29 Apr 2017]
327. Ruther T, Hagedorn D, Schiela K, et al. Nicotine delivery efficiency of first- and second-generation e-cigarettes and its impact on relief of craving during the acute phase of use. *Int J Hyg Environ Health* 2018;221(2):191-98. doi: 10.1016/j.ijheh.2017.10.012 [published Online First: 28 Oct 2018]
328. Cobb CO, Lopez AA, Soule EK, et al. Influence of electronic cigarette liquid flavors and nicotine concentration on subjective measures of abuse liability in young adult cigarette smokers. *Drug Alcohol Depend* 2019;203:27-34. doi: 10.1016/j.drugalcdep.2019.05.024
329. Hughes JR, Peters EN, Callas PW, et al. Withdrawal symptoms from e-cigarette abstinence among adult never-smokers: A pilot experimental study. *Nicotine Tob Res* 2019c;22(5):740–46. doi: 10.1093/ntr/ntz169
330. Vena A, Miloslavich K, Cao D, et al. Cue salience of the use of an electronic nicotine delivery system (ENDS) device marketed to women. *Addict Behav* 2020;100:106116. doi: 10.1016/j.addbeh.2019.106116
331. Stiles MF, Campbell LR, Graff DW, et al. Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: implications for abuse liability. *Psychopharmacology (Berl)* 2017;234(17):2643-55. doi: 10.1007/s00213-017-4665-y
332. Hobkirk AL, Nichols TT, Foulds J, et al. Changes in resting state functional brain connectivity and withdrawal symptoms are associated with acute electronic cigarette use. *Brain Res Bull* 2018;138:56-63. doi: 10.1016/j.brainresbull.2017.05.010

333. Solingapuram Sai K, K., Zuo Y, Rose JEYG, et al. Rapid brain nicotine uptake from electronic cigarettes. *J Nucl Med* 2019 doi: 10.2967/jnumed.119.230748 [published Online First: 01 Nov 2019]
334. Russo C, Cibella F, Caponnetto P, et al. Evaluation of post cessation weight gain in a 1-year randomized smoking cessation trial of electronic cigarettes. *Sci Rep* 2016;6:18763 doi: 10.1038/srep18763
335. Hiler M, Breland A, Spindle T, et al. Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. *Exp Clin Psychopharmacol* 2017;25(5):380-92. doi: 10.1037/pha0000140
336. Flouris AD, Poulianiti KP, Chorti MS, et al. Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol* 2012;50(10):3600-03. doi: 10.1016/j.fct.2012.07.025
337. Farsalinos KE, Tsiapras D, Kyrzopoulos S, et al. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC Cardiovasc Disord* 2014b;14:78. doi: 10.1186/1471-2261-14-78
338. Szoltysek-Boldys I, Sobczak A, Zielinska-Danch W, et al. Influence of inhaled nicotine source on arterial stiffness [Zmiana sztywności tętnic w zależności od źródła inhalowanej nikotyny]. *Przegl Lek* 2014;71(11):572-75.
339. Cooke WH, Pokhrel A, Dowling C, et al. Acute inhalation of vaporized nicotine increases arterial pressure in young non-smokers: A pilot study. *Clin Auton Res* 2015;25(4):267-70. doi: 10.1007/s10286-015-0304-z
340. Yan X, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul Toxicol Pharmacol* 2015;71(1):24-34. doi: 10.1016/j.yrtph.2014.11.004
341. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, et al. Electronic cigarette smoking increases aortic stiffness and blood pressure in young smokers. *J Am Coll Cardiol* 2016;67(23):2802-03. doi: 10.1016/j.jacc.2016.03.569
342. Carnevale R, Sciarretta S, Violi F, et al. Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest* 2016;150(3):606-12. doi: 10.1016/j.chest.2016.04.012
343. Moheimani RS, Bhetraratana M, Peters KM, et al. Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. *J Am Heart Assoc* 2017;6(9):e006579. doi: 10.1161/JAHA.117.006579 [published Online First: 20 Sep 2017]
344. Mastrangeli S, Carnevale R, Cavarretta E, et al. Predictors of oxidative stress and vascular function in an experimental study of tobacco versus electronic cigarettes: A post hoc analysis of the SUR-VAPES 1 Study. *Tob Induc Dis* 2018;16(May):18. doi: 10.18332/tid/89975 [published Online First: 08 May 2018]
345. Chaumont M, de Becker B, Zaher W, et al. Differential effects of e-cigarette on microvascular endothelial function, arterial stiffness and oxidative stress: A randomized crossover trial. *Sci Rep* 2018a;8:10378. doi: 10.1038/s41598-018-28723-0 [published Online First: 10 Jul 2018]
346. George J, Hussain M, Vadiveloo T, et al. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *J Am Coll Cardiol* 2019;74(25):3112-20. doi: 10.1016/j.jacc.2019.09.067
347. Antoniewicz L, Bosson JA, Kuhl J, et al. Electronic cigarettes increase endothelial progenitor cells in the blood of healthy volunteers. *Atherosclerosis* 2016;255:179-85. doi: 10.1016/j.atherosclerosis.2016.09.064
348. Farsalinos K, Cibella F, Caponnetto P, et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern Emerg Med* 2016;11(1):85-94. doi: 10.1007/s11739-015-1361-y
349. Cossio R, Cerra ZA, Tanaka H. Vascular effects of a single bout of electronic cigarette use. *Clin Exp Pharmacol Physiol* 2020;47(1):3-6. doi: 10.1111/1440-1681.13180 [published Online First: 18 Sep 2019]
350. Franzen KF, Willig J, Cayo TS, et al. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. *Vasc Med* 2018;23(5):419-25. doi: 10.1177/1358863X18779694 [published Online First: 09 Jul 2018]
351. Spindle TR, Talih S, Hiler MM, et al. Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography. *Drug Alcohol Depend* 2018;188:193-99. doi: 10.1016/j.drugalcdep.2018.03.042
352. Sumartiningsih S, Lin HF, Lin JC. Cigarette smoking blunts exercise-induced heart rate response among young adult male smokers. *Int J Environ Res Public Health* 2019;16(6):1032. doi: 10.3390/ijerph16061032
353. Fogt DL, Levi MA, Rickards CA, et al. Effects of acute vaporized nicotine in non-tobacco users at rest and during exercise. *Int J Exerc Sci* 2016;9(5):607-15.
354. Nocella C, Biondi-Zoccai G, Sciarretta S, et al. Impact of tobacco versus electronic cigarette smoking on platelet function. *Am J Cardiol* 2018;122(9):1477-81. doi: 10.1016/j.amjcard.2018.07.029
355. Chaumont M, van de Borne P, Bernard A, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchanges disturbances: Results from two randomized clinical trials. *Am J Physiol Lung Cell Mol Physiol* 2019;316(5):L705-L19. doi: 10.1152/ajplung.00492.2018

356. Antoniewicz L, Brynedal A, Hedman L, et al. Acute effects of electronic cigarette inhalation on the vasculature and the conducting airways. *Cardiovasc Toxicol* 2019;19(5):441-50. doi: 10.1007/s12012-019-09516-x
357. Pywell MJ, Wordsworth M, Kwasnicki RM, et al. The effect of electronic cigarettes on hand microcirculation. *J Hand Surg Am* 2018;43(5):432-38. doi: 10.1016/j.jhsa.2017.12.003
358. Chaumont M, Tagliatti V, Channan EM, et al. Short halt in vaping modifies cardio-respiratory parameters and urine metabolome: a randomized trial. *Am J Physiol Lung Cell Mol Physiol* 2020;318(2):L331-L44. doi: 10.1152/ajplung.00268.2019
359. Campagna D, Cibella F, Cappeonnetto P, et al. Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *Eur J Clin Invest* 2016;46(8):698-706. doi: 10.1111/eci.12651
360. Cibella F, Campagna D, Caponnetto P, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)* 2016;130(21):1929-37. doi: 10.1042/CS20160268
361. Boulay M-E, Henry C, Bosse Y, et al. Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. *Respir Res* 2017;18(1):33. doi: 10.1186/s12931-017-0518-9
362. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol* 2013;25(2):91-101. doi: 10.3109/08958378.2012.758197
363. Ferrari M, Zanasi A, Nardi E, et al. Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers. *BMC Pulm Med* 2015;15:120. doi: 10.1186/s12890-015-0106-z
364. D'Ruiz CD, O'Connell G, Graff DW, et al. Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regul Toxicol Pharmacol* 2017;87:36-53. doi: 10.1016/j.yrtph.2017.05.002
365. Coppeta L, Magrini A, Pietroiusti A, et al. Effects of smoking electronic cigarettes on pulmonary function and environmental parameters. *Open Public Health J* 2018;11(1):360-68. doi: 10.2174/1874944501811010360
366. Barna S, Rozsa D, Varga J, et al. First comparative results about the direct effect of traditional cigarette and e-cigarette smoking on lung alveolocapillary membrane using dynamic ventilation scintigraphy. *Nucl Med Commun* 2019;40(2):153-58. doi: 10.1097/MNM.0000000000000957
367. Vardavas CI, Anagnostopoulos N, Kougias M, et al. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 2012;141(6):1400-06. doi: 10.1378/chest.11-2443
368. Dicpinigaitis PV, Chang AL, Dicpinigaitis AJ, et al. Effect of electronic cigarette use on the urge-to-cough sensation. *Nicotine Tob Res* 2016;18(8):1763-65. doi: 10.1093/ntr/ntw021
369. Kumral TL, Salturk Z, Yildirim G, et al. How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance? *B-ENT* 2016;12(1):17-21.
370. Chaumont M, Bernard A, Pochet S, et al. High-wattage e-cigarettes induce tissue hypoxia and lower airway injury: A randomized clinical trial. *Am J Respir Crit Care Med* 2018b;198(1):123-26. doi: 10.1164/rccm.201711-2198LE
371. Lappas AS, Tzortzi AS, Konstantinidi EM, et al. Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma. *Respirology* 2018;23(3):291-97. doi: 10.1111/resp.13180
372. Staudt MR, Salit J, Kaner RJ, et al. Altered lung biology of healthy never smokers following acute inhalation of e-cigarettes. *Respiratory Res* 2018;19:78. doi: 10.1186/s12931-018-0778-z [published Online First: 14 May 2018]
373. Chatterjee S, Tao JQ, Johncola A, et al. Acute exposure to e-cigarettes causes inflammation and pulmonary endothelial oxidative stress in nonsmoking, healthy young subjects. *Am J Physiol Lung Cell Mol Physiol* 2019;317(2):L155-L66. doi: 10.1152/ajplung.00110.2019
374. Kerr DMI, Brooksbank KJM, Taylor RG, et al. Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study. *J Hypertens* 2019;37(1):154-66. doi: https://journals.lww.com/jhypertension/Fulltext/2019/01000/Acute_effects_of_electronic_and_tobacco_cigarettes.24.aspx
375. Reuther WJ, Hale B, Matharu J, et al. Do you mind if I vape? Immediate effects of electronic cigarettes on perfusion in buccal mucosal tissue - a pilot study. *Br J Oral Maxillofac Surg* 2016;54(3):338-41. doi: 10.1016/j.bjoms.2015.12.001
376. Wadia R, Booth V, Yap HF, et al. A pilot study of the gingival response when smokers switch from smoking to vaping. *Br Dent J* 2016;221(11):722-26. doi: 10.1038/sj.bdj.2016.914
377. Papaseit E, Farre M, Graziano S, et al. Monitoring nicotine intake from e-cigarettes: measurement of parent drug and metabolites in oral fluid and plasma. *Clin Chem Lab Med* 2017;55(3):415-23. doi: 10.1515/cclm-2016-0405 [published Online First: 25 Aug 2016]

378. van Staden SR, Groenewald M, Engelbrecht R, et al. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. *S Afr Med J* 2013;103(11):864-68. doi: 10.7196/samj.6887
379. McRobbie H, Phillips A, Goniewicz ML, et al. Effects of switching to electronic cigarettes with and without concurrent smoking on exposure to nicotine, carbon monoxide, and acrolein. *Cancer Prev Res (Phila)* 2015;8(9):873-78. doi: 10.1158/1940-6207.CAPR-15-0058
380. O'Connell G, Graff DW, D'Ruiz CD. Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Toxicol Mech Methods* 2016;26(6):443-54. doi: 10.1080/15376516.2016.1196282
381. Goniewicz ML, Gawron M, Smith DM, et al. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: A longitudinal within-subjects observational study. *Nicotine Tob Res* 2017;19(2):160-67. doi: 10.1093/ntr/ntw160
382. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control* 2017;26(e1):e23-e28. doi: 10.1136/tobaccocontrol-2016-053041 [published Online First: 21 Mar 2017]
383. Czoli CD, Fong GT, Goniewicz ML, et al. Biomarkers of exposure among "dual users" of tobacco cigarettes and electronic cigarettes in Canada. *Nicotine Tob Res* 2018;21(9):1259-66. doi: 10.1093/ntr/nty174
384. Round EK, Chen P, Taylor AK, et al. Biomarkers of tobacco exposure decrease after smokers switch to an e-cigarette or nicotine gum. *Nicotine Tob Res* 2018;21(9):1239-47. doi: 10.1093/ntr/nty140 [published Online First: 10 Sep 2018]
385. Beatrice F, Massaro G. Exhaled carbon monoxide levels in forty resistant to cessation male smokers after six months of full switch to electronic cigarettes (e-cigs) or to a tobacco heating systems (THS). *Int J Environ Res Public Health* 2019;16(20):15. doi: 10.3390/ijerph16203916 [published Online First: 15 Oct 2019]
386. Yuki D, Sakaguchi C, Kikuchi A, et al. Pharmacokinetics of nicotine following the controlled use of a prototype novel tobacco vapor product. *Regul Toxicol Pharmacol* 2017;87:30-35. doi: 10.1016/j.yrtph.2017.05.005
387. Hajek P, Goniewicz ML, Phillips A, et al. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. *Nicotine Tob Res* 2015;17(2):175-79. doi: 10.1093/ntr/ntu153
388. St Helen G, Liakoni E, Nardone N, et al. Comparison of systemic exposure to toxic and/or carcinogenic volatile organic compounds (VOCs) during vaping, smoking, and abstention. *Cancer Prev Res (Phila)* 2020;31(2):153-62. doi: 10.1158/1940-6207.CAPR-19-0356
389. Valentine GW, Jatlow PI, Coffman M, et al. The effects of alcohol-containing e-cigarettes on young adult smokers. *Drug Alcohol Depend* 2016b;159:272-76. doi: 10.1016/j.drugalcdep.2015.12.011
390. Poulianiti K, Karatzaferi C, Flouris AD, et al. Antioxidant responses following active and passive smoking of tobacco and electronic cigarettes. *Toxicol Mech Methods* 2016;26(6):455-61. doi: 10.1080/15376516.2016.1196281
391. Norton KJ, June KM, O'Connor RJ. Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. *Tob Induc Dis* 2014;12(October):17. doi: 10.1186/1617-9625-12-17
392. Cravo AS, Bush J, Sharma G, et al. A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regul Toxicol Pharmacol* 2016;81 Suppl 1:S1-S14. doi: 10.1016/j.yrtph.2016.10.003
393. Walele T, Bush J, Koch A, et al. Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-life setting. *Regul Toxicol Pharmacol* 2018;92:226-38. doi: 10.1016/j.yrtph.2017.12.010
394. Rosbrook K, Green BG. Sensory effects of menthol and nicotine in an e-cigarette. *Nicotine Tob Res* 2016;18(7):1588-95. doi: 10.1093/ntr/ntw019
395. Riggare S, Unruh KT, Sturr J, et al. Patient-driven n-of-1 in Parkinson's disease. Lessons learned from a placebo-controlled study of the effect of nicotine on dyskinesia. *Methods Inf Med* 2017;56(S01):e123-28. doi: 10.3414/ME16-02-0040
396. Lee MS, Rees VW, Koutrakis P, et al. Cardiac autonomic effects of secondhand exposure to nicotine from electronic cigarettes: An exploratory study. *Environ Epidemiol* 2019b;3(1):e033. doi: 10.1097/EE9.0000000000000033
397. Melstrom P, Sosnoff C, Koszowski B, et al. Systemic absorption of nicotine following acute secondhand exposure to electronic cigarette aerosol in a realistic social setting. *Int J Hyg Environ Health* 2018;221(5):816-22. doi: 10.1016/j.ijheh.2018.05.003 [published Online First: 29 May 2018]

398. Aokage T, Tsukahara K, Fukuda Y, et al. Heat-not-burn cigarettes induce fulminant acute eosinophilic pneumonia requiring extracorporeal membrane oxygenation. *Respir Med Case Rep* 2019;26:87-90. doi: 10.1016/j.rmcr.2018.12.002 [published Online First: 04 Dec 2018]
399. Kamada T, Yamashita Y, Tomioka H. Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. *Respirol Case Rep* 2016;4(6):e00190. doi: 10.1002/rcr2.190
400. Lee A, Lee K-S, Park H. Association of the use of a heated tobacco product with perceived stress, physical activity, and internet use in Korean adolescents: A 2018 national survey. *Int J Environ Res Public Health* 2019c;16(6):965. doi: 10.3390/ijerph16060965 [published Online First: 18 Mar 2019]
401. Roethig HJ, Kinser RD, Lau RW, et al. Short-term exposure evaluation of adult smokers switching from conventional to first-generation electrically heated cigarettes during controlled smoking. *J Clin Pharmacol* 2005;45(2):133-45. doi: 10.1177/0091270004271253
402. Picavet P, Haziza C, Lama N, et al. Comparison of the pharmacokinetics of nicotine following single and ad libitum use of a tobacco heating system or combustible cigarettes. *Nicotine Tob Res* 2016;18(5):557-63. doi: 10.1093/ntr/ntv220
403. Unverdorben M, der Bijl A, Potgieter L, et al. Effects of levels of cigarette smoke exposure on symptom-limited spiroergometry. *Prev Cardiol* 2007;10(2):83-91. doi: 10.1111/j.1520-037x.2007.06036.x
404. Unverdorben M, van der B, Potgieter L, et al. Effects of different levels of cigarette smoke exposure on prognostic heart rate and rate--pressure-product parameters. *J Cardiovasc Pharmacol Ther* 2008;13(3):175-82. doi: 10.1177/1074248408321571
405. Roethig HJ, Feng S, Liang Q, et al. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation electrically heated cigarette smoking system. *J Clin Pharmacol* 2008;48(5):580-91. doi: 10.1177/0091270008315316
406. Munjal S, Koval T, Muhammad R, et al. Heart rate variability increases with reductions in cigarette smoke exposure after 3 days. *J Cardiovasc Pharmacol Ther* 2009;14(3):192-98. doi: 10.1177/1074248409340340
407. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. *Regul Toxicol Pharmacol* 2012;64(2 Suppl):S74-84. doi: 10.1016/j.yrtph.2012.08.006
408. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect. *Biomarkers* 2015;20(6-7):404-10. doi: 10.3109/1354750X.2015.1094135
409. Lüdicke F, Picavet P, Baker G, et al. Effects of switching to the Menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: A randomized, controlled, open-label, multicenter study in ssequential confinement and ambulatory settings (Part 2). *Nicotine Tob Res* 2018a;20(2):173-82. doi: 10.1093/ntr/ntx028 [published Online First: 21 Apr 2017]
410. Unverdorben M, Mostert A, Munjal S, et al. Acute effects of cigarette smoking on pulmonary function. *Regul Toxicol Pharmacol* 2010;57(2-3):241-46. doi: 10.1016/j.yrtph.2009.12.013
411. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst* 2011;103(24):1827-39. doi: 10.1093/jnci/djr483
412. Tricker AR, Stewart AJ, Leroy CM, et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 3: eight-day randomized clinical trial in the UK. *Regul Toxicol Pharmacol* 2012a;64(2 Suppl):S35-44. doi: 10.1016/j.yrtph.2012.08.010
413. Tricker AR, Jang IJ, Martin L, et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 4: eight-day randomized clinical trial in Korea. *Regul Toxicol Pharmacol* 2012b;64(2 Suppl):S45-53. doi: 10.1016/j.yrtph.2012.08.013
414. Tricker AR, Kanada S, Takada K, et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 5: 8-Day randomized clinical trial in Japan. *Regul Toxicol Pharmacol* 2012c;64(2 Suppl):S54-63. doi: 10.1016/j.yrtph.2012.08.003
415. Tricker AR, Kanada S, Takada K, et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. *Regul Toxicol Pharmacol* 2012d;64(2 Suppl):S64-73. doi: 10.1016/j.yrtph.2012.08.007
416. Sakaguchi C, Kakehi A, Minami N, et al. Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. *Regul Toxicol Pharmacol* 2014;69(3):338-47. doi: 10.1016/j.yrtph.2014.04.016
417. Haziza C, de La Bourdonnaye G, Merlet S, et al. Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement. *Regul Toxicol Pharmacol* 2016a;81:489-99. doi: 10.1016/j.yrtph.2016.09.014

418. Haziza C, de La Bourdonnaye G, Skiada D, et al. Evaluation of the Tobacco Heating System 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. *Regul Toxicol Pharmacol* 2016b;81 Suppl 2:S139-S50. doi: 10.1016/j.yrtph.2016.11.003
419. Haziza C, de La Bourdonnaye G, Donelli A, et al. Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the Menthol Tobacco Heating System 2.2 for three months (Part 1). *Nicotine Tob Res* 2020;22(4):539–48. doi: 10.1093/ntr/ntz013 [published Online First: 05 Feb 2019]
420. Ludicke F, Haziza C, Weitkunat R, et al. Evaluation of biomarkers of exposure in smokers switching to a carbon-heated tobacco product: A controlled, randomized, open-label 5-day exposure study. *Nicotine Tob Res* 2016;18(7):1606-13. doi: 10.1093/ntr/ntw022
421. Ludicke F, Baker G, Magnette J, et al. Reduced exposure to harmful and potentially harmful smoke constituents with the Tobacco Heating System 2.1. *Nicotine Tob Res* 2017;19(2):168-75. doi: 10.1093/ntr/ntw164 [published Online First: 01 Jul 2016]
422. Lüdicke F, Picavet P, Baker G, et al. Effects of switching to the Tobacco Heating System 2.2 Menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: A randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 1). *Nicotine Tob Res* 2018b;20(2):161-72. doi: 10.1093/ntr/ntw287 [published Online First: 21 Apr 2017]
423. Gale N, McEwan M, Eldridge AC, et al. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: A randomized, controlled study in healthy Japanese subjects. *Nicotine Tob Res* 2018;21(9):1220-27. doi: 10.1093/ntr/nty104 [published Online First: 15 Jun 2018]
424. O'Brien D, Long J, Quigley J, et al. Electronic cigarette use and smoking initiation in adolescents: An evidence review. Dublin: Health Research Board, 2020.
425. Quigley J, Long J, Kennelly H, et al. Electronic cigarettes and smoking cessation: An evidence review. Dublin: Health Research Board, 2020.
426. McNeill A, Brose LS, Calder R, et al. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England London, England: Public Health England; 2018 [243pp]. Available from: https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review.
427. Peruga A, World Health Organization Regional Ofice for Europe. Heated tobacco products: a brief Copenhagan: World Health Organization Regional Ofice for Europe,; 2020b [16 pp]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2020/heated-tobacco-products-a-brief-2020.
428. Pisinger C, Dossing M. A systematic review of health effects of electronic cigarettes. *Prev Med* 2014;69:248-60. doi: 10.1016/j.ypmed.2014.10.009
429. Canadian Agency for Drugs and Technologies in Health (CADTH). Electronic cigarettes for the reduction or cessation of smoking: Clinical utility, safety, and guidelines Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health (CADTH),; 2017 [updated 05 Sep 2017. Available from: https://cadth.ca/electronic-cigarettes-reduction-or-cessation-smoking-clinical-utility-safety-and-guidelines-0 accessed RB1130-000.
430. Byrne S, Brindal E, Williams G, et al. E-cigarettes, smoking and health: A literature review update Australia: Commonwealth Scientific and Industrial Research Organisation (CSIRO) 2018 [394pp]. Available from: https://www.csiro.au/en/Research/BF/Areas/Nutrition-and-health/Public-health-and-wellbeing/Case-studies/E-cigarettes-report.
431. Bals R, Boyd J, Esposito S, et al. Electronic cigarettes: A task force report from the European Respiratory Society. *Eur Resp J* 2019;53(2):1801151. doi: 10.1183/13993003.01151-2018
432. Peruga A, World Health Organization Regional Ofice for Europe. Electronic nicotine and non-nicotine delivery systems: a brief Copenhagan,: World Health Organization Regional Ofice for Europe,; 2020a [20 pp]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2020/electronic-nicotine-and-non-nicotine-delivery-systems-a-brief-2020.
433. Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. *Prev Med* 2014;69:248-60. doi: 10.1016/j.ypmed.2014.10.009
434. El Dib R, Suzumura EA, Akl EA, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis. *BMJ Open* 2017;7(2):e012680. doi: 10.1136/bmjopen-2016-012680
435. Evans SE, Hoffman AC. Electronic cigarettes: Abuse liability, topography and subjective effects. *Tob Control* 2014;23 Suppl 2:ii23-29. doi: 10.1136/tobaccocontrol-2013-051489
436. Glasser A, Abudayyeh H, Cantrell J, et al. Patterns of e-cigarette use among youth and young adults: Review of the impact of e-cigarettes on cigarette smoking. *Nicotine Tob Res* 2019;21(10):1320-30. doi: 10.1093/ntr/nty103

437. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: A systematic review. *Am J Prev Med* 2017;52(2):e33-e66. doi: 10.1016/j.amepre.2016.10.036
438. Hartmann-Boyce J, McRobbie H, Bullen C, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016;9:Cd010216. doi: 10.1002/14651858.CD010216.pub3
439. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: A systematic review and meta-analysis. *Lancet Respir Med* 2016;4(2):116-28. doi: 10.1016/s2213-2600(15)00521-4
440. Khoudigian S, Devji T, Lytvyn L, et al. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: A systematic review and a meta-analysis. *Int J Public Health* 2016;61(2):257-67. doi: 10.1007/s00038-016-0786-z
441. Knight-West O, Bullen C. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil* 2016;7:111-18. doi: 10.2147/sar.S94264 [published Online First: 18 Aug 2016]
442. Liu X, Lu W, Liao S, et al. Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)* 2018;97(19):e0324. doi: 10.1097/md.0000000000010324
443. Livingston CJ, Freeman RJ, Costales VC, et al. Electronic nicotine delivery systems or e-cigarettes: American College of Preventive Medicine's practice statement. *Am J Prev Med* 2019;56(1):167-78. doi: 10.1016/j.amepre.2018.09.010
444. Malas M, van der Tempel J, Schwartz R, et al. Electronic cigarettes for smoking cessation: A systematic review. *Nicotine Tob Res* 2016;18(10):1926-36. doi: 10.1093/ntr/ntw119
445. O'Leary R, MacDonald M, Stockwell T, et al. Clearing the air: A systematic review on the harms and benefits of e-cigarettes and vapour devices Victoria, Canada: Canadian Institute for Substance Use Research, University of Victoria; 2017 [Available from: https://www.uvic.ca/research/centres/cisur/projects/active/projects/e-cigs.php.
446. Rahman MA, Hann N, Wilson A, et al. E-cigarettes and smoking cessation: Evidence from a systematic review and meta-analysis. *PLoS One* 2015;10(3):e0122544. doi: 10.1371/journal.pone.0122544 [published Online First: 30 Mar 2015]
447. Health Information and Quality Authority, (HIQA). Health technology assessment (HTA) of smoking cessation interventions Dublin, Ireland: Health Information and Quality Authority (HIQA); 2017 [Available from: https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf.
448. Wells C, Farrah K. Electronic cigarettes for the reduction or cessation of smoking: clinical utility, safety, and guidelines [Rapid Response]. Ottowa, Canada: Canadian Agency for Drugs and Technologes in Health (CADTH); 2017 [Available from: https://www.cadth.ca/electronic-cigarettes-reduction-or-cessation-smoking-clinical-utility-safety-and-guidelines-0.
449. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf* 2014a;5(2):67-86. doi: 10.1177/2042098614524430
450. Vapor4Life. Vapor King Single Logo Auto Battery Northbrook, Illinois: Vapor4Life; 2012 [Available from: https://www.webcitation.org/65G0NCbj8.
451. Valeo Laboratories. [Homepage] Meldorf, Germany: Valeo Laboratories,; 2020 [Available from: http://www.e-liquid-wholesale.com.
452. Food and Drug Administration. Harmful and potentially harmful constituents in tobacco products and tobacco smoke: Established list [website] Washington DC, USA: Food and Drug Administration, ; 2012 [updated 2019. Available from: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list accessed 14 Feb 2020.

Appendices

Appendix 1: Literature search strategies and results

List of databases and resources used

1. Ovid MEDLINE
2. Cochrane Library: Cochrane CENTRAL and Cochrane Reviews
3. Ovid PsycINFO
4. Elsevier Embase
5. NHS NIHR PROSPERO
6. PAHO/WHO/Bireme LILACS
7. Google Scholar
8. CORE.ac.uk (Open University/JISC)
9. List of reviews and reports used for citation searching

Results from each database			
Database	**Articles before deduplication**	**Articles after de-duplication**	**Duplicates excluded from each database**
Total	14,676	6,510	8,166
Ovid MEDLINE	3,874	3,690	184
Wiley Cochrane Central	527	274	253
Wiley Cochrane Database of Systematic Reviews	14	12	2
Ovid PsycINFO	1,519	369	1,150
Elsevier Embase	4,212	1,391	2,821
NHS NIHR PROSPERO	93	93	0
PAHO/WHO/Bireme LILACS	4,042	558	3,506
Google Scholar	200	43	157
CORE.ac.uk	192	80	112

1. Ovid MEDLINE search strategy and results

Ovid MEDLINE: E-cigarettes and heat-not-burn tobacco products	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 12, 2019
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and heat-not-burn tobacco products (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search term	Results
E-cigarettes	1	Vaping/	291
	2	Electronic Nicotine Delivery Systems/	2293
	3	"Nebulizers and Vaporizers"/ and (nicotine or tobacco).mp.	155
	4	e-cig$.mp.	3087
	5	Ecig$.mp.	80
	6	(Vape or vaping or vaper or vapers).mp.	853
	7	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	77
	8	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	3496
	9	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	55
	10	(mods adj5 (tobacco or nicotine)).mp.	2
	11	Juul$.mp.	40
	12	(e-juice$ or e-liquid$).mp.	392
	13	(cig-a-like$ or cigalike$ or ciga-like$).mp.	36
	14	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	19
	15	(ENNDS or electronic non-nicotine delivery).mp.	3
	16	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
	17	or/1-16	4520
Heat-not-burn tobacco products	18	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	118
	19	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	83
	20	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	13
	21	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	2
	22	(IQOS or iFuse or Ploom).mp.	70
	23	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	1
	24	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "kuumutatud tubakas" or "pinainit na tabako" or "lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	11
	25	or/18-24	218
E-cigarettes or heat-not-burn tobacco products	26	17 or 25	4645
	27	animals/ not humans.sh.	4536484

Basic animal and cell studies search	28	exp animals, laboratory/ or exp Animal experimentation/ or exp Models, animal/ or Disease Models, Animal/ or exp Animal Diseases/	1563266
	29	(animal adj2 (model$ or stud$ or experiment$ or laboratory)).ti,ab,kf.	231870
	30	(Cat or cats or feline or dog or dogs or canine or rat or rats or Wistar or Sprague-Dawley or rodent$ or mouse or mice or murine or zebrafish or fish or chicken$ or horse$ or rabbit$ or "C. elegans" or caenorhabditis elegans or nematod$ or Xenopus or bird or birds or reptil$ or livestock or larva$).ti,ab,kf.	3615741
	31	exp In Vitro Techniques/ or exp Biological Assays/ or exp cells, cultured/ or exp clinical laboratory techniques/ or Chemistry techniques, analytical/ or chemistry techniques, synthetic/	4144439
	32	("in vitro" or biological assay$ or cell culture or cultured cells or cell lines or cell transformation assay$).ti,ab,kf.	1414252
	33	27 or 28 or 29 or 30 or 31 or 32	8519746
(E-cigarettes or heat-not-burn tobacco products) NOT cell or animal studies	34	26 not 33	4284
Publication type	35	(comment or editorial or note).pt.	1105825
	36	(reply or commentary or comment or editorial).ti.	135049
	37	35 or 36	1158642
(((E-cigarettes or heat-not-burn tobacco products**) NOT cell or animal studies) NOT letters, commentary)**	**38**	**34 not 37**	**3874**

2. Cochrane Database of Systematic Reviews and Cochrane Central search strategy and results

Cochrane Library: E-cigarettes and HeatNotBurn devices	
Database	John Wiley & Sons Cochrane Library including Cochrane Database of Systematic Reviews and Cochrane CENTRAL
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)

Concept	Search number	Search terms	Results
E-cigarettes	#1	MeSH descriptor: [Vaping] explode all trees	10
	#2	MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees	72
	#3	MeSH descriptor: [Nebulizers and Vaporizers] explode all trees	2218
	#4	((nicotine OR tobacco)):ti,ab,kw	10856
	#5	#3 AND #4	31
	#6	(e-cig*):ti,ab,kw	309
	#7	(ecig*):ti,ab,kw	309
	#8	((vape OR vaping OR vaper OR vapers)):ti,ab,kw	66
	#9	(((vaporise OR vaporised OR vaporiser OR vaporize OR vaporized OR vaporizer) NEAR/3 (cigarette* OR nicotine))):ti,ab,kw	18
	#10	(((electric or electronic) NEAR/2 (nicotine or tobacco or smoking or cig*))):ti,ab,kw	321
	#11	((e-sigaret* OR "e-sígarett*" OR E-Zigarette* OR "cigarette* électronique*" OR "L'e-cigarette" OR vapoteuse* OR "cigarrill* electrónico*" OR sigarett* elettronic* OR sigarett* elettronik* OR sigarett* elettroniche* OR elektronik* sigar* OR e-savuke* OR e-rokok* OR rokok* elektronik* OR e-papieros* OR e-ugwayi)):ti,ab,kw	9
	#12	((mods NEAR/5 (nicotine OR tobacco))):ti,ab,kw	0
	#13	(Juul*):ti,ab,kw	11
	#14	(e-juic* OR e-liquid*):ti,ab,kw	48
	#15	((cig-a-like* OR cigalike* OR ciga-like*)):ti,ab,kw	4
	#16	(e-hookah* OR "electronic hookah" OR "electronic hookahs" OR "hookah pen" OR "hookah pens"):ti,ab,kw	2
	#17	(ENNDS OR "electronic non-nicotine delivery"):ti,ab,kw	0
	#18	((NMNDS AND nicotin*)):ti,ab,kw	0
	#19	(non-medicinal nicotine delivery system*):ti,ab,kw	0
	#20	#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	463
Heat-not-burn tobacco products	#21	("heated tobacco" OR "tobacco heating"):ti,ab,kw	43
	#22	(Heated tobacco product* OR tobacco heating product* OR tobacco heating system*):ti,ab,kw	70
	#23	("heat-not-burn" OR "heat not burn" OR "heat notburn" OR "heatnot burn" OR "heatnotburn"):ti,ab,kw	6
	#24	(Heatsticks OR heat-sticks OR "heat sticks" OR tobacco sticks OR Neosticks):ti,ab,kw	9
	#25	(IQOS or iFuse or Ploom):ti,ab,kw	17
	#26	((Vapotage OR "tabac chauffé" OR "verhitte tabak" OR "riscaldatori di tabacco" OR "tabacco riscaldato" OR "erhitzter Tabak" OR "verhit tabak" OR "zahřátý tabák" OR "opvarmet tobak" OR "oppvarmet tobakk" OR "uppvärmd tobak" OR "kuumutatud tubakas" OR "pinainit na tabako" OR "lämmitetty tupakka" OR "shan taba mai tsanani" OR "hitað tóbak" OR "apsildāmā tabaka" OR "tembakau dipanaskan" OR "šildomas tabakas" OR "tembakau yang dipanaskan" OR "te taakapa" OR "podgrzewany tytoń" OR "tabaco aquecido" OR "încălzit tutunul" or "zahriaty tabak" OR "ogrevani tobak" OR "tabaco caliente" OR "ısıtılmış tütün" OR "ugwayi ovuthayo" OR "thuốc lá nóng")):ti,ab,kw	7
	#27	((HEETS or Fiit or glo) NEAR/3 (tobacco or nicotine or smok*)):ti,ab,kw	1
	#28	(("electrically-heated smoking system" AND (nicotin* OR tobacco*))):ti,ab,kw	1
	#29	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	103
E-cigarettes OR heat-not-burn tobacco products	#30	#20 OR #29	541 (of which 14 reviews, 527 central)

3. Ovid PsycINFO search strategy and results

Ovid PsycINFO: E-cigarettes and HeatNotBurn devices	
Database	Ovid PsycINFO
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	NOTE: did not remove animal or publication type items from PsycINFO as after testing, very few animal studies, and publication types filter removed useful items also.
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search terms	Results
E-cigarettes	1	exp Electronic cigarettes/	897
	2	((Nebulizer$ or Vaporizer$) adj5 (nicotine or tobacco)).mp.	14
	3	e-cig$.mp.	1188
	4	Ecig$.mp.	59
	5	(Vape or vaping or vaper or vapers).mp.	252
	6	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	33
	7	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	1215
	8	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	1
	9	(mods adj5 (tobacco or nicotine)).mp.	1
	10	Juul$.mp.	27
	11	(e-juice$ or e-liquid$).mp.	76
	12	(cig-a-like$ or cigalike$ or ciga-like$).mp.	21
	13	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	6
	14	(ENNDS or electronic non-nicotine delivery).mp.	0
	15	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
	16	or/1-15	1510
Heat-not-burn tobacco products	17	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	6
	18	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	14
	19	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	2
	20	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	0
	21	(IQOS or iFuse or Ploom).mp.	6
	22	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	0
	23	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "tabaco aquecido" or "kuumutatud tubakas" or "pinainit na tabako" or	2

		"lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	
	24	or/17-23	20
E-cigarettes OR heat-not-burn tobacco products	25	16 or 24	1518

4. Elsevier Embase search strategy and results

Elsevier Embase: E-cigarettes and HeatNotBurn devices	
Database	Elsevier Embase
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search terms	Results
E-cigarettes	#1	'vaping'/exp OR 'vaping'	1,014
	#2	'electronic cigarette'/exp	4,468
	#3	'e cig*':ti,ab,kw	3,604
	#4	ecig*:ti,ab,kw	212
	#5	vape:ti,ab,kw OR vaping:ti,ab,kw OR vaper:ti,ab,kw OR vapers:ti,ab,kw	803
	#6	vapori?e$ NEAR/3 (cigarette* OR nicotine)	79
	#7	((electric OR electronic) NEAR/2 (cig* OR nicotine OR tobacco OR smoking)):ti,ab,kw	3,046
	#8	'e sigaret*':ti,ab,kw OR 'e sígarett*':ti,ab,kw OR 'e zigarette*':ti,ab,kw OR 'cigarette* électronique*':ti,ab,kw OR 'l e cigarette':ti,ab,kw OR vapoteuse*:ti,ab,kw OR 'cigarrill* electrónico*':ti,ab,kw OR 'sigarett* elettronic*':ti,ab,kw OR 'sigarett* elettronik*':ti,ab,kw OR 'sigarett* elettroniche*':ti,ab,kw OR 'elektronik* sigar*':ti,ab,kw OR 'e savuke*':ti,ab,kw OR 'e rokok*':ti,ab,kw OR 'rokok* elektronik*':ti,ab,kw OR 'e papieros*':ti,ab,kw OR 'e ugwayi':ti,ab,kw	9
	#9	(mods NEAR/5 (tobacco OR nicotin* OR smoking OR cigarette)):ti,ab,kw	2
	#10	'juul*':ti,ab,kw	42

	#11	'e juice*':ti,ab,kw OR 'e liquid*':ti,ab,kw	548
	#12	'cig-a-like*':ti,ab,kw OR 'cigalike*':ti,ab,kw OR 'ciga-like*':ti,ab,kw OR 'cig-alike':ti,ab,kw	86
	#13	'e hookah*':ti,ab,kw OR 'electronic hookah*':ti,ab,kw OR 'electric hookah*':ti,ab,kw OR 'hookah pen*':ti,ab,kw OR 'e-shisha':ti,ab,kw OR 'electronic shisha':ti,ab,kw OR 'electric shisha':ti,ab,kw	17
	#14	'ennds':ti,ab,kw OR 'electronic non-nicotine delivery':ti,ab,kw	6
	#15	nmnds:ti,ab,kw AND nicotine:ti,ab,kw	0
		#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	5,675
Hurn products	#17	'heated tobacco':ti,ab,kw OR 'tobacco heating':ti,ab,kw	183
	#18	'heat-not-burn':ti,ab,kw OR 'heat not burn':ti,ab,kw OR 'heat notburn':ti,ab,kw OR 'heatnot burn':ti,ab,kw	104
	#19	'heatsticks':ti,ab,kw OR 'heatstick':ti,ab,kw OR 'heat-stick':ti,ab,kw OR 'heat-sticks':ti,ab,kw OR 'tobacco sticks':ti,ab,kw OR 'tobacco stick':ti,ab,kw OR 'neostick':ti,ab,kw OR neosticks:ti,ab,kw	17
	#20	((heets OR fiit OR glo OR ifuse) NEAR/3 (tobacco OR nicotine OR smok*)):ti,ab,kw	5
	#21	iqos:ti,ab,kw OR ploom:ti,ab,kw	55
	#22	'electrically-heated smoking system':ti,ab,kw AND (nicotin*:ti,ab,kw OR tobacco*:ti,ab,kw)	1
	#23	vapotage:ti,ab,kw OR 'tabac chauffé':ti,ab,kw OR 'verhitte tabak':ti,ab,kw OR 'riscaldatori di tabacco':ti,ab,kw OR 'tabacco riscaldato':ti,ab,kw OR 'erhitzter tabak':ti,ab,kw OR 'verhit tabak':ti,ab,kw OR 'zahřátý tabák':ti,ab,kw OR 'opvarmet tobak':ti,ab,kw OR 'oppvarmet tobakk':ti,ab,kw OR 'uppvärmd tobak':ti,ab,kw OR 'kuumutatud tubakas':ti,ab,kw OR 'pinainit na tabako':ti,ab,kw OR 'lämmitetty tupakka':ti,ab,kw OR 'shan taba mai tsanani':ti,ab,kw OR 'hitað tóbak':ti,ab,kw OR 'apsildāmā tabaka':ti,ab,kw OR 'tembakau dipanaskan':ti,ab,kw OR 'šildomas tabakas':ti,ab,kw OR 'tembakau yang dipanaskan':ti,ab,kw OR 'te taakapa':ti,ab,kw OR 'podgrzewany tytoń':ti,ab,kw OR 'tabaco aquecido':ti,ab,kw OR 'încălzit tutunul':ti,ab,kw OR 'zahriaty tabak':ti,ab,kw OR 'ogrevani tobak':ti,ab,kw OR 'tabaco caliente':ti,ab,kw OR 'ısıtılmış tütün':ti,ab,kw OR 'ugwayi ovuthayo':ti,ab,kw OR 'thuốc lá nóng':ti,ab,kw	1
	#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	263
E-cigarettes OR heat-not-burn tobacco products	#25	#16 OR #24	5,850
Animal, in vitro or cell line studies	#26	'animal'/exp NOT 'human'/exp	5,227,728
	#27	'experimental animal'/exp	623,633
	#28	'animal experiment'/exp	2,359,962
	#29	'nonhuman'/exp	5,756,936

	#30	'animal model'/exp	1,244,803
	#31	'animal tissue, cells or cell components'/exp	3,618,529
	#32	'veterinary clinical trial'/exp	2
	#33	animal NEAR/2 (model* OR stud* OR experiment* OR laboratory)	2,716,111
	#34	cat:ti,ab,kw OR cats:ti,ab,kw OR feline:ti,ab,kw OR dog:ti,ab,kw OR dogs:ti,ab,kw OR canine:ti,ab,kw OR rat:ti,ab,kw OR rats:ti,ab,kw OR wistar:ti,ab,kw OR 'sprague dawley':ti,ab,kw OR rodent*:ti,ab,kw OR mouse:ti,ab,kw OR mice:ti,ab,kw OR murine:ti,ab,kw OR zebrafish:ti,ab,kw OR fish:ti,ab,kw OR chicken*:ti,ab,kw OR horse*:ti,ab,kw OR rabbit*:ti,ab,kw OR 'c. elegans':ti,ab,kw OR 'caenorhabditis elegans':ti,ab,kw OR nematod*:ti,ab,kw OR xenopus:ti,ab,kw OR bird:ti,ab,kw OR birds:ti,ab,kw OR reptil*:ti,ab,kw OR livestock:ti,ab,kw OR larva*:ti,ab,kw	4,327,895
	#35	'human tissue, cells or cell components'/exp	2,434,643
	#36	'bioassay'/exp	250,786
	#37	'in vitro study'/exp	5,605,074
	#38	'in vitro':ti,ab,kw OR 'biological assay*':ti,ab,kw OR 'cell culture':ti,ab,kw OR 'cultured cells':ti,ab,kw OR 'cell lines':ti,ab,kw OR 'cell transformation assay*':ti,ab,kw	1,769,394
	#39	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	11,508,677
(E-cigarettes OR heat-not-burn tobacco products) NOT animal, in vitro or Cell lines	#40	#25 NOT #39	4,844
Editorials, replies, commentaries	#41	'editorial'/exp	603,392
		#42 'note'/exp	706,258
	#43	('editorial'/it OR 'note'/it) AND ([editorial]/lim OR [note]/lim)	1,337,186
	#44	'reply':ti	77,815
	#45	commentary:ti	51,142
	#46	editorial:ti	72,014
	#47	note:ti	28,805
	#48	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	1,506,914
((E-cigarettes OR HnB) NOT animal, in vitro or Cell lines) NOT	#49	#40 NOT #48	4,212

Editorials, replies, commentaries	

5. NHS NIHR PROSPERO

NHS NIHR PROSPERO E-cigarettes and **heat-not-burn tobacco products**	
Database	NHS NIHR PROSPERO https://www.crd.york.ac.uk/prospero/#searchadvanced
Date of Search	15.04.2019
Note	"All status reviews, All fields" used
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	None
Publication types	None

Concept	Search number	Search terms	Search results
E-cigarettes	#1	e-cig*	62
	#2	ecig*	3
	#3	MeSH DESCRIPTOR Vaping EXPLODE ALL TREES	6
	#4	e-juic*	2
	#5	e-liquid*	4
	#6	cig-a-like OR cigalike OR cig-alike OR ciga-like	0
	#7	e-hookah	5
	#8	juul	26
	#9	vape	11
	#10	vaping	22
	#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	92
HnB	#12	"heated tobacco" OR "tobacco heating"	2
	#13	"heat-not-burn" OR "heat not burn" OR "heat notburn" OR "heatnot burn"	2
	#14	heatsticks OR "heat-sticks" OR "tobacco sticks" OR neosticks	0
	#15	iqos OR ploom OR iFuse	1
	#16	"electrically heated smoking system" AND tobacco	0
	#17	#16 OR #15 OR #14 OR #13 OR #12	4
E-cigarettes OR heat-not-burn tobacco products	#18	#17 OR #11	93

6. LILACS (Latin American and Caribbean Health Sciences Literature)

LILACS: E-cigarettes and **heat-not-burn tobacco products** devices	
Database	PAHO/WHO/Bireme LILACS (Including databases: (LILACS, IBECS, CUMED, BDENF – Nursing, BBO – Dentistry, WHO IRIS, PAHO-IRIS, Index Psychology - Scientific journals, MedCarib)
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Search number	Search terms	Search results
1	(tw:(("E-cigarette" OR "E-cigarettes" OR “ecigarette” or “ecigarettes” OR vaping OR vape OR "electronic nicotine" OR "cig-a-like" OR "e-hookah" OR "E-liquid" OR "E-juice")))	
2	“cigarrillo electrónico” OR “cigarrillo electrónico” OR OR “e-cigarros” OR “e-cigarro” OR "cigarette électronique" OR "cigarettes électroniques" OR “e-sigaretten” OR “een sigaret” OR “sigaretta elettronica” OR “sigarette elettroniche”	
3	"heated tobacco" OR "tobacco heating" OR "heat-not-burn" OR "heat not burn" OR IQOS OR heatsticks OR "heat-sticks" OR "tobacco sticks"	
4	Vapotage OR "tabac chauffé" OR "verhitte tabak" OR "riscaldatori di tabacco" OR "tabacco riscaldato" OR "erhitzter Tabak" OR "verwarmde tabak" OR "tabaco aquecido"	
		Database results Show in graphical form: total n=4061 MEDLINE (4019) IBECS (21) LILACS (14) DeCS - Descriptors in Health Sciences (2) WHO IRIS (2) BRISA/RedTESA (1) LIS -Health Information Locator (1) PAHO-IRIS (1)

7. Google scholar

Google Scholar: E-cigarettes and **heat-not-burn tobacco products**	
Search Engine and Browser	Google Scholar on Firefox 66
Date of Search	15.04.2019
Note	Due to the simple search interface, reduced searches were used for the two research concepts. Limitation of using Google Scholar include limited search faceting and the unknown algorithm sorting the results.
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and heat-not-burn tobacco products (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Excluded patents

Concept	Search terms	Results	Results considered
E-cigarettes	(E-cigarette OR ecigarette OR Vape OR Vaping OR Vaper OR e-juice OR e-liquid OR e-hookah)	About 28,700 results (0.56 sec)	First 100 results (first 10 pages of results)
heat-not-burn tobacco products	"heated tobacco" OR "tobacco heating" OR "heat-not-burn" OR "heat not burn" OR "IQOS" OR "heatsticks" OR "heat-sticks" OR "tobacco sticks"	About 4,140 results (0.34 sec)	First 100 results (first 10 pages of results)

8. CORE.ac.uk

CORE.ac.uk E-cigarettes and **heat-not-burn tobacco products**			
Repository	CORE.ac.uk (The Open University and JISC)		
Date of Search	15.04.2019		
Note	Due to the simple search interface, reduced searches were used. Search terms were limited to e-cigarette and vaping terms.		
Age limits	None used in the search		
Geographic limits	None		
Language limits	None used in the search.		
Date limits	None		
Study types	None excluded in the search		
Publication types	None excluded in the search		
Search terms	**Results**	**Selected**	**After deduplication**
title:((E-cigarette OR ecigarette OR Vape OR Vaping OR Vaper))	Over 2 million results	First 100 (default sorting: relevance)	100
title:(("heat-not-burn" OR "tobacco heating" OR "heated tobacco" OR "heat not burn" OR IQOS OR heatnotburn)	158	100 (default sorting: relevance)	92

9. List of reviews and reports used for citation searching in supplemental searches

Reviews

1. El Dib R, Suzumura EA, Akl EA, et al.[434] Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. *BMJ Open* 2017;7(2):e012680. doi: 10.1136/bmjopen-2016-012680 [published Online First: 2017/02/27]
2. Evans SE, Hoffman AC.[435] Electronic cigarettes: abuse liability, topography and subjective effects. *Tob Control* 2014;23 Suppl 2:ii23-9. doi: 10.1136/tobaccocontrol-2013-051489 [published Online First: 2014/04/16]
3. Glasser A, Abudayyeh H, Cantrell J, et al.[436] Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. *Nicotine & Tobacco Research* 2018;21(10):1320-30. doi: 10.1093/ntr/nty103
4. Glasser AM, Collins L, Pearson JL, et al.[437] Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med* 2017;52(2):e33-e66. doi: 10.1016/j.amepre.2016.10.036
5. Hartmann-Boyce J, McRobbie H, Bullen C, et al.[438] Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016;9:Cd010216. doi: 10.1002/14651858.CD010216.pub3
6. Kalkhoran S, Glantz SA.[439] E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med* 2016;4(2):116-28. doi: 10.1016/s2213-2600(15)00521-4
7. Khoudigian S, Devji T, Lytvyn L, et al.[440] The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. *Int J Public Health* 2016;61(2):257-67. doi: 10.1007/s00038-016-0786-z
8. Knight-West O, Bullen C.[441] E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil* 2016;7:111-8. doi: 10.2147/sar.S94264
9. Liu X, Lu W, Liao S, et al.[442] Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)* 2018;97(19):e0324. doi: 10.1097/md.0000000000010324
10. Livingston CJ, Freeman RJ, Costales VC, et al.[443] Electronic nicotine delivery systems or e-cigarettes: American College of Preventive Medicine's Practice Statement. *Am J Prev Med* 2019;56(1):167-78. doi: 10.1016/j.amepre.2018.09.010
11. Malas M, van der Tempel J, Schwartz R, et al.[444] Electronic cigarettes for smoking cessation: A Systematic Review. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016;18(10):1926-36. doi: 10.1093/ntr/ntw119
12. O'Leary R, MacDonald M, Stockwell T, et al.[445] Clearing the air: A systematic review on the harms and benefits of e-cigarettes and vapour devices Victoria, Canada: Canadian Institute for Substance Use Research, University of Victoria, 2017.
13. Rahman MA, Hann N, Wilson A, et al.[446] E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. *PloS one* 2015;10(3):e0122544. doi: 10.1371/journal.pone.0122544

Reports

1. Bals R, Boyd J, Esposito S, et al.[431] Electronic cigarettes: a task force report from the European Respiratory Society. *Eur Resp J* 2019;53:1801151. doi: 10.1183/13993003.01151-2018
2. Health Information and Quality Authority, (HIQA).[447] Health technology assessment (HTA) of smoking cessation interventions [Internet] Dublin, Ireland: Health Information and Quality Authority (HIQA); 2017 [Available from: https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf
3. McNeill A, Brose L, Calder R, et al.[426] Evidence review of e-cigarettes and heated tobacco products 2018 A report commissioned by Public Health England London, England: Public Health England; 2018 [Available from: https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review .
4. National Academies of Sciences, Engineering, Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems.[6] Public health consequences of e-cigarettes. Washington (DC): National Academies of Sciences, Engineering, Medicine; 2018 [Available from: http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx.
5. Wells C, Farrah K.[448] Electronic cigarettes for the reduction or cessation of smoking: clinical utility, safety, and guidelines [Rapid response]. Ottowa, Canada: Canadian Agency for Drugs and Technologies in Health (CADTH); 2017 [Available from: https://www.cadth.ca/electronic-cigarettes-reduction-or-cessation-smoking-clinical-utility-safety-and-guidelines-0.

Appendix 2: E-cigarette and vaping associated lung injury

Twelve papers[132 134 136 137 138 135 139 166 171 172 247 287] reported on the outbreak of lung injury associated with e-cigarettes or vaping, a phenomena known as e-cigarette and vaping associated lung injury (E-VALI or VALI). The papers represented findings which occurred between June and October 2019 across a range of American states. The papers focused on one or more of the following areas: case presentation and clinical signs and symptoms, including hospital stay and treatments, diagnostic criteria and associated technologies, development of algorithms or guidelines as diagnostic aids, and pathogenesis and disease aetiology. Five of the papers summarised findings from Centers for Disease Control and Prevention's (CDC) news alerts on the topic, the Morbidity and Mortality Weekly Report Early Release (MMWR). The news alerts summarised report clinical findings, survey data estimating prevalence of e-cigarette use and EVALI, and laboratory findings. [166 171 172 247 287]

The team of authors represented a large number of disciplines investigating the phenomenon that included: clinical practitioners, radiologists, histopathologists, haematologists, microbiologists, public health specialists, epidemiologists, and surveillance information systems officers.

The geographical distribution identified cases from 20 of the 50 states. Specifically Utah, [132 166 172] Arizona, Florida and Minnesota,[134] California and Wisconsin,[136] New York,[137] Georgia,[138] Ohio, Tennessee,[135] Pennsylvania,[139] California, Connecticut, Hawaii, Illinois,[166 247 287] Maryland, Michigan, Minnesota, Texas, Wisconsin,[166] and North Carolina[171]. Apart from the CDC survey data papers the number of subjects reported on ranged from 5 to 83. Where detailed, the age of presenting patients ranged from 14 to 66 years with an average ages of 19 to 35 years reported (three did not report on age). Two papers did not report sex, three papers reporting findings on males only and the percentage of females in the study population varied from 17% to 41%.

The World Health Organization was the only review recent enough to cover lung injury and reported that up to 7 January 2020, more than 2,500 cases had been reported to Centers for Disease Control and Prevention from 50 states in the USA, and just under 60 deaths had been confirmed in 27 states.[432] The World Health Organization stated that the Centers identified the causal agent as Vitamin E acetate which is used as an additive, most notably as a thickening agent in tetrahydrocannabinol-containing e-cigarette, or vaping, products.[432]

Clinical presentation

The E-VALI presenting constitutional symptoms were predominantly respiratory and or gastrointestinal[132] in nature; but other non-specific symptoms were also reported. Respiratory morbidity presented both as acute and subacute[134] but most frequently demonstrated a rapid development with subsequent acute lung injuries.[136] Episodes of subacute organising pneumonia (inflammation of the bronchioles and surrounding tissue in the lungs) developing over a period of days to weeks and arising from hard metals in e-cigarette use was also reported.[136] The main respiratory signs and symptoms included: features of dyspnoea, fever, cough,[137] pleuritic pain,[135] sputum, haemoptysis (the coughing of blood the respiratory tract below the level of the larynx),[138] shortness of breath,[135] and non-productive cough and chest pain.[166] The main gastrointestinal symptoms included emesis (vomiting),[137 138 135] nausea, diarrhoea,[138 135 166] and abdominal pain.[138 166 135] The range of systemic symptoms reported included: fever (subjunctive),[166] sweats, chills and myalgias (pain in a muscle or group of muscles), weight loss, fatigue or malaise,[138] and headache.[135] In addition, a range of miscellaneous complaints where patients had made previous health-care visit(s) for symptoms suggested to be potentially related to the use of e-cigarettes were noted. These included: sore throat, nasal congestion, headache, epistaxis (nosebleed), odynophagia (painful swallowing) and leg and back pain.[138] A number of presenting cases required hospital admission and a sub-set of these required intensive case treatment and intubation. The majority of cases recovered, though some with varying report regarding residual lung damage, and there were some fatalities.

Diagnostic criteria and technologies

A range of imaging chest imaging techniques were employed in the diagnostic process: including computed tomography (CT) and X-ray. One paper, from Wisconsin and California, reported four imaging patterns that correlated with pathological findings attributable to vaping.[136] These included: acute eosinophilic pneumonia (accumulation of eosinophils, one type of white blood cell, in the lungs), diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia (a form of lung inflammation that develops when lipids enter the bronchial tree).[136] Most of the patterns had basilar-predominant consolidation and ground-glass opacity, often with areas of lobular or subpleural sparing.[136]

A second paper, from Wisconsin and Illinois, which reported the CT results of 48 of 53 cases found findings were abnormal in 100% of patients. Opacities in both lungs were reported as present, with the ground-glass opacities in both lungs and subpleural sparing.[138] In eight of the patients with CT imaging, there were four cases of pneumomediastinum, five cases of pleural effusions, and one case of pneumothorax. One patient had both a pneumomediastinum and a pneumothorax, and one patient had both a pneumomediastinum and pleural effusion.[138]

Patients with EVALI in Pennsylvania has similar chest X-ray results that is their X-ray films showed bilateral, multifocal alveolar opacifications.[139] CT scans supported these finding revealing multi-lobar ground glass opacities with subpleural sparing.[139] CT and X-ray imaging techniques were complemented by other imaging techniques such as bronchoscopy which allowed the biopsy of tissue samples for histological examination.

Finding from clinics spanning four states, Minnesota, Florida, Illinois and Arizona, reviewed lung biopsies from patients whom had a history of vaping (71% with marijuana or cannabis oils) and were clinically suspected to have EVALI.[134] Histopathological findings showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, and/or organizing pneumonia, usually bronchiolocentric accompanied by bronchiolitis. No histologic findings were specific, but foamy macrophages and pneumocyte vacuolization were seen in all cases.[134]

A coordinated public health investigation, in Wisconsin and Illinois, following reports of pulmonary disease associated with the use of e-cigarettes examined the data of 24 patients who underwent bronchoalveolar lavage.[138] A total of seven cytology reports on bronchoalveolar-lavage specimens stained with oil red O noted lipid-laden macrophages. Patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was reported. Although the features of e-cigarette use that were responsible for injury were not identified, the cluster of illnesses was deemed to represent an emerging clinical syndrome or syndromes.[138]

Algorithms development or guidelines as diagnostic aids

The Wisconsin Department of Health Services and the Illinois Department of Public Health released their first health alert notices on 25 July 2019 and 2 August 2019, respectively, to inform clinicians of the initial cases and to request reporting of possible cases to their local health departments.[138] Their original outbreak case definition accompanying this report was further refined in coordination with the CDC and the Council for State and Territorial Epidemiologists.[135]

The criteria for a 'confirmed case' were as follows:

1. Using an e-cigarette or dabbing during the 90 days before symptom onset
2. Pulmonary infiltrate on chest radiograph or ground glass opacities on chest CT
3. Absence of pulmonary infection on initial workup. Minimum criteria include negative respiratory viral panel, influenza polymerase chain reaction, or rapid test if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for Streptococcus pneumoniae and Legionella, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, human immunodeficiency virus (HIV)–related opportunistic respiratory infections if appropriate) must be negative.

4. No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).[135]

Pathogenesis and disease aetiology

The authors of several papers investigated potential causal factors for E-VALI and mechanisms of disease. The report from Blount *et al.*[166] was the first to identify a potential toxicant of concern (vitamin E acetate) in biologic specimens obtained from EVALI patients. The authors stated findings provided direct evidence of vitamin E acetate at the primary site of injury among EVALI patients and are consistent with Food and Drug Administration product testing and media reports of state public health laboratory testing documenting vitamin E acetate in product samples used by EVALI patients. Other diluents and additives of concern (e.g., plant oils, medium chain triglyceride oil, petroleum distillates, and diluent terpenes) were not detected in bronchoalveolar lavage fluid specimens from EVALI patients. Vitamin E acetate was detected in all specimens in their analysis of a convenience sample of 29 EVALI case associated bronchoalveolar lavage specimens. However, the authors stated that additional studies are needed, including comparison with bronchoalveolar lavage fluid specimens from healthy volunteers and animal studies using controlled exposures to establish whether a causal link exists between this exposure and EVALI. They also suggest however, it is possible that more than one compound or ingredient could be a cause of lung injury, and evidence is not yet sufficient to rule out the contribution of other toxicants to EVALI.[166] Navon *et al.* noted from their survey findings that EVALI patients had higher odds of reporting exclusive and more frequent use of THC-containing products including Dank Vales (a class of largely counterfeit THC-containing products) and of obtaining these products from informal sources, such as a dealer, off the street, or from a friend.[287]

Table 66 E-cigarette and vaping associated lung injury (EVALI) extracted from surveillance papers

Author(s), year	Possible benefit or harm	Surveillance papers on respiratory diseases
		EVALI
Blagev *et al.*[132] 2019	Harm	In this multicentre, prospective, observational, cohort study the authors reported on risk factors of e-cigarette, or vaping, and products used by patients presenting at the Intermountain Healthcare, an integrated health system in Utah, USA, between June 27 and Oct 4, 2019. Telecritical care, based in Salt Lake City, Utah, USA, was used as the central repository for case validation, public reporting, and system-wide dissemination of expertise, which included a proposed diagnosis and treatment guideline for lung injury associated with e-cigarettes or vaping In total, 60 patients presented with lung injury associated with e-cigarettes or vaping at 13 hospitals or outpatient clinics in the integrated health system. 33 (55%) of 60 were admitted to an intensive care unit (ICU). 53 (88%) of 60 patients presented with constitutional symptoms, 59 (98%) with respiratory symptoms, and 54 (90%) with gastrointestinal symptoms. 54 (90%) of 60 were given antibiotics and 57 (95%) were given steroids. Six (10%) of 60 patients were readmitted to an ICU or hospital within 2 weeks, three (50%) of whom had relapsed with vaping or e-cigarette use. Of 26 patients who were followed up within 2 weeks, despite clinical and radiographic improvement in all, many had residual abnormalities on chest radiographs (ten [67%] of 15) and pulmonary function tests (six [67%] of nine). Two patients died and lung injury associated with e-cigarettes or vaping was thought to be a contributing factor, but not the cause of death, for both. The authors concluded that **lung injury associated with e-cigarettes or vaping is an emerging illness** associated with severe lung injury as well as with constitutional and gastrointestinal symptoms. Increased awareness has led to identification of a broad spectrum of severity of illness in patients who were treated with antibiotics and steroids. Despite improvement, at short-term follow-up, many patients had residual abnormalities.

		Device and products: Length of use: <1 year 10/23 (43%), 1–<2 years 4/23 (17%), 2–<3 years 6/23 (26%) and ≥3 years 3/23 (13%) Type of device used: Disposable e-cigarette 5/23 (22%), Reusable device for liquids 16/22 (73%), Reusable device for wax or dry herbs 9/23 (39%), Vape rig (for competitive vaping and stronger vape) 5/22 (23%), Vaping salts 3/23 (13%) Reported inhalation device: Juul (nicotine) 7 (26%), Smok (nicotine) 2 (7%), Nicotine E-Juice (various brands) 7 (26%), Golden Gorilla (tetrahydrocannabinol) 4 (15%), Smart Cart (tetrahydrocannabinol) 3 (11%), Cereal (tetrahydrocannabinol) 1 (4%), Dank Vapes (tetrahydrocannabinol) 6 (22%), Rove (tetrahydrocannabinol) 6 (22%) Other brands of inhalation device: (tetrahydrocannabinol), 11 (41%) Where vape liquid purchased: A Utah vape shop 4 (15%), Dealer 4 (15%), Online dealer or social media app 7 (26%), Out of state dispensary 2 (7%), Friend 5 (19%), Convenience store 2 (7%) Vape liquid or e-liquid used: Prefilled cartridges 18/23 (78%), Dank Vapes 10/22 (45%), A variety of liquids 16/20 (80%), Premade liquid 13/22 (59%), Nicotine 17/25 (68%), Tetrahydrocannabinol oil 22/25 (88%), Marijuana 10/21 (48%), Cannabidiol oil 10/23 (44%), Synthetic marijuana 18/21 (86%), Mixed own vape liquid 1/21 (5%) If using tetrahydrocannabinol, using for medicinal reasons 7/11 (64%).
Butt *et al.* [134] 2019	Harm	The authors reviewed lung biopsies from 17 patients (13 men; median age=35 years [range: 19–67 years]), all of whom had a history of vaping (71% with marijuana or cannabis oils) and were clinically **suspected to have vaping-associated lung injury**. Presentation was acute or subacute in all cases, with bilateral pulmonary opacities; all but two patients presented in 2019. 11 met the criteria for a 'confirmed' diagnosis of vaping-related lung injury; the remaining 6 met the criteria for a 'probable' designation. In all cases, histopathological findings showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organising pneumonia. No histological findings were specific, but foamy macrophages and pneumocyte vacuolisation were seen in all cases and may be useful diagnostic clues in an appropriate clinical context. Pigmented macrophages were sometimes present but were never a dominant feature. Neutrophils were often prominent, but eosinophils were rare, and granulomas were not seen. In two cases, bronchioloalveolar lavage fluid was available and contained abundant foamy macrophages. Despite treatment with glucocorticoids and maximum supportive care, two patients with diffuse alveolar damage died Device and products: Not reported
Henry *et al.*[136] 2019	Harm	The authors reported imaging patterns that they had identified from 19 cases of **vaping-associated lung disease** which they had seen in a clinical setting. All met the case definition of vaping-associated lung injury, which includes "abnormalities on chest imaging". The authors identified four imaging patterns that correlated with pathological findings attributable to vaping, including acute eosinophilic pneumonia, diffuse alveolar damage, organising pneumonia, and lipoid pneumonia. In addition, some cases were associated with variegated imaging patterns. Through clinical and pathological investigations, patterns of giant cell interstitial pneumonia, hypersensitivity pneumonitis, and diffuse alveolar haemorrhage were identified. Although the variety of imaging patterns suggests different mechanisms of injury, and more patterns will probably be reported, most of the patterns have basilar-predominant consolidation and ground glass opacity, often with areas of lobular or subpleural sparing. The authors noted that rapidly developing acute lung injuries are associated with inhalational injuries, have overlapping pathological and imaging findings, and have been reported to occur with vaping. Hypersensitivity pneumonitis is an immune response to an environmental antigen, but the antigens related to vaping are unknown. Lipoid pneumonia is an inflammatory response to the presence of lipids within the alveolar space and typically results from aspiration of

		hydrocarbons or oil-based products, but it has now been seen with vaping. The authors have not observed the computed tomographic finding of fat attenuation in the lung, which is a hallmark of lipoid pneumonia, in these cases of vaping-associated lung injury. Not all cases are acute; organising pneumonia often develops sub-acutely, over a period of days to weeks, and the one case of giant cell interstitial pneumonia that was correlated with hard metals in e-cigarettes developed over a period of 6 months. Device and products: Not reported
Kalininskiy *et al.* [137] 2019	Harm	The authors reported on 12 cases treated for suspected **e-cigarette, or vaping, product use associated with lung injury** at their medical centre between 6 June and 15 September 2019. 10 (83%) patients had dyspnoea, fever, and vomiting, and 9 (75%) had cough. 11 (92%) patients reported the use of e-cigarette cartridges containing tetrahydrocannabinol oil. Although eight (67%) patients required admission to the intensive care unit for hypoxaemic respiratory failure, no deaths occurred. The median hospitalisation duration was 7 days. All patients completing follow-up (6 [50%]) had resolution of previous chest abnormalities. The authors highlighted the importance of ruling out infection and other cardiopulmonary conditions before making a presumptive diagnosis of e-cigarette, or vaping, product use-associated lung injury. 11 patients reported vaping a tetrahydrocannabinol product. Device and products specifically substance use: Tetrahydrocannabinol vaping 11 (92%), Nicotine vaping 7 (58%), Cannabis use (non-vape) 5 (42%), Cannabidiol vaping 1 (8%), Nicotine vaping only 1 (8%), Tobacco cigarettes 1 (8%)
Layden *et al.* [138] 2020	Harm	The authors reported on work commenced in July 2019 by the Wisconsin Department of Health Services and the Illinois Department of Public Health which receive, and process reports of **pulmonary disease associated with the use of e-cigarettes (vaping).** The authors defined cases as persons who reported use of e-cigarette devices and related products in the 90 days before symptom onset and who had pulmonary infiltrates on imaging, and whose illnesses were not attributed to other causes. Medical record abstraction and case patient interviews were conducted with the use of standardised tools. There were 53 cases, 83% of whom were male; the median age of the patients was 19 years. The majority of the patients presented with respiratory symptoms (98%), gastrointestinal symptoms (81%), and constitutional symptoms (100%). All case patients had bilateral infiltrates on chest imaging. A total of 94% of the patients were hospitalised, and 32% underwent intubation and mechanical ventilation; one death was reported. A total of 84% of the patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was reported. Device and products specifically substance use: All patients had a history of use of e-cigarettes and related products within the 90 days before symptom onset, and 94% of those with data (32 of 34 patients) regarding the date of last use reported vaping in the week before symptom onset. Most patients (29 of 33 patients [88%]) reported at least daily e-cigarette use. Of the 41 patients who were extensively interviewed, 61% reported use of nicotine products, 80% reported use of tetrahydrocannabinol products, and 7% reported use of cannabidiol products. A total of 37% of the patients reported using tetrahydrocannabinol products only, whereas 17% reported using nicotine-containing products only. A total of 44% of the patients reported using both nicotine and tetrahydrocannabinol products. Patients reported using 14 distinct brands of tetrahydrocannabinol products and 13 brands of nicotine products in a wide range of flavours. The most common tetrahydrocannabinol product that was reported was marketed under the “Dank Vape” label (reported by 24 of 41 interviewed patients [59%]). Patients reported use of a number of different e-cigarette devices to aerosolize these

		products. Of the 41 patients who were extensively interviewed, seven reported smoking combustible cigarettes as well.
Mukhopadhyay *et al* [135] 2020	Harm	The authors described findings from the lung biopsies of eight male patients (aged 19–61 years) who had a **vaping-associated pulmonary illness**. The biopsies were negative for infection in all cases, and there was no evidence for other aetiologies. Imaging showed diffuse bilateral ground glass opacities in all patients. Seven of the patients recovered with corticosteroid therapy and one died. Lung biopsies (seven transbronchial, one surgical) showed acute lung injury, including organising pneumonia and/or diffuse alveolar damage. Common features were fibroblast plugs, hyaline membranes, fibrinous exudates, type 2 pneumocyte hyperplasia, and interstitial organisation. Some cases featured a sparse interstitial chronic inflammatory infiltrate. Although macrophages were present within the airspaces in all cases, this feature was not prominent, and findings typical of exogenous lipoid pneumonia were absent. The authors concluded that the histopathology of acute pulmonary illness was related to e-cigarette use (vaping) and was characterised by acute lung injury patterns, supporting the contention that vaping can cause severe lung damage Device and products specifically substance use: (individual practices reported): 90% tetrahydrocannabinol, tetrahydrocannabinol (brand: “Dank”) and nicotine; recent refill of cartridge with 90% tetrahydrocannabinol, tetrahydrocannabinol /marijuana (vaping) and marijuana wax (dabbing), tetrahydrocannabinol (cannabis oil), Purified tetrahydrocannabinol tetrahydrocannabinol, tetrahydrocannabinol and nicotine, 93% tetrahydrocannabinol
Triantafyllou *et al.*[139] 2019	Harm	The authors reported on six young men who presented with high fever and a variety of respiratory and gastrointestinal symptoms, including dyspnoea, non-productive cough, chest and abdominal pain, nausea, vomiting, and watery diarrhoea. All patients reported **regular use of vaporised cannabis and nicotine products**, and the most recent exposure ranged between 3 and 9 days prior to presentation. Four of the patients used the same type of cannabis solution. Chest radiographs demonstrated **bilateral, multifocal alveolar opacifications**. Computed tomography scans revealed multilobar ground glass opacities with subpleural sparing. Two patients underwent bronchoscopy with bronchoalveolar lavage. Microbial cultures were negative in the bronchoalveolar lavage. Extensive infectious workup came back negative for every patient, and most received corticosteroid treatment. No fatalities occurred. Device and products: Not described
Blount et al.[168] 2019	Harm	The authors investigated a national outbreak of lung injury associated with e-cigarette, or vaping, product use. Based on data collected as of 15 October 2019, 86% of 867 e-cigarette, or vaping, product use-associated lung injury patients reported using tetrahydrocannabinol-containing products in the 3 months preceding symptom onset. Analyses of tetrahydrocannabinol-containing product samples by Food and Drug Administration and state public health laboratories have identified potentially harmful constituents in these products, such as vitamin E acetate, medium-chain triglyceride oil, and other products. Vitamin E acetate, in particular, might be used as an additive in the production of e-cigarette, or vaping, products; it can also be used as a thickening agent in tetrahydrocannabinol products. Inhalation of vitamin E acetate might impair lung function. The Centers for Disease Control and Prevention, the Food and Drug Administration, state and local health departments, and multiple public health and clinical partners investigated a national outbreak of e-cigarette, or vaping, product use–associated lung injury. Findings here are (lower case b required in following word)

		Based on data collected as of 15 October 2019, 86% of 867 e-cigarette, or vaping, product use-associated lung injury patients reported using tetrahydrocannabinol-containing products in the 3 months preceding symptom onset. Analyses of tetrahydrocannabinol-containing product samples by Food and Drug Administration and state public health laboratories have identified potentially harmful constituents in these products, such as vitamin E acetate, medium-chain triglyceride oil, and other products. Vitamin E acetate, in particular, might be used as an additive in the production of e-cigarette, or vaping, products; it can also be used as a thickening agent in tetrahydrocannabinol products. Inhalation of vitamin E acetate might impair lung function. Device and products: Among 23 patients for whom self-reported tetrahydrocannabinol use information was available,20 reported using tetrahydrocannabinol-containing products. Tetrahydrocannabinol or its metabolites were detected in 23 of 28 patient bronchoscopy and bronchoalveolar lavage samples, including in those of three patients who said they did not use tetrahydrocannabinol products. Nicotine metabolites were detected in 16 of 26 patient bronchoscopy and bronchoalveolar lavage specimens. Results for plant oils, medium chain triglyceride oil, petroleum distillates, and diluent terpenes were all below analyte-specific levels of detection (typically in the low ng/mL range).
Davidson et al.[173] 2019	Harm	The authors reported on more than 200 possible cases of acute lung injury potentially associated with vaping reported from 25 states. During July and August 2019, five patients were identified at two hospitals in North Carolina with acute lung injury potentially associated with e-cigarette use. The patients were adults aged 18–35 years, and all experienced several days of worsening dyspnoea, nausea, vomiting, abdominal discomfort, and fever. All patients demonstrated tachypnoea with increased difficulty with breathing on examination, hypoxaemia (pulse oximetry <90% on room air), and bilateral lung infiltrates on chest X-ray. All five patients shared a history of recent use of marijuana oils or concentrates in e-cigarettes. All of the products used were electronic vaping pens/e-cigarettes that had refillable chambers or interchangeable cartridges with tetrahydrocannabinol vaping concentrates or oils, which were all purchased on the street. Three of the patients also used nicotine-containing e-cigarettes, and two of the patients smoked marijuana or conventional combustible tobacco cigarettes, although none used other illicit drugs. All five patients were hospitalised for hypoxaemic respiratory failure. All of the patients survived. Device and products: Not reported
Lewis et al.[174] 2019	Harm	The Utah Department of Health (UDOH) detailed medical abstractions for a subset of 83 patients in Utah who presented with lung injury. Detailed medical abstractions were completed for 79 patients (95%). Of the 79 patients, 70 (89%) were hospitalised, 39 (49%) required breathing assistance, and many reported pre-existing respiratory and mental health conditions. Among 53 interviewed patients, all of whom reported using e-cigarette, or vaping, products within 3 months of the acute lung injury, 49 (92%) reported using any products containing tetrahydrocannabinol, 35 (66%) reported using any nicotine-containing products, and 32 (60%) reported using both. Product sample testing at the Utah Public Health Laboratory showed evidence of vitamin E acetate in 17 of 20 (89%) tetrahydrocannabinol-containing cartridges, which were provided by 6 of the 53 interviewed patients. Device and products: Among 53 interviewed patients, all of whom reported using e-cigarette, or vaping, products within 3 months of acute lung injury, 49 (92%) reported using any products containing tetrohydrocannabinol, the principal psychoactive component of cannabis; 35 (66%) reported using any nicotine-containing products, and 32 (60%) reported using both. Most tetrohydrocannabinol-containing products were acquired from informal

		sources such as friends or illicit in-person and online dealers. Tetrohydrocannabinol containing products were most commonly used one to five times per day, whereas nicotine-containing products were most commonly used >25 times per day.
Ghinai et al.[247] 2019	Harm	In July 2019, the Illinois Department of Public Health and the Wisconsin Department of Health Services launched a coordinated epidemiologic investigation after receiving reports of several cases of lung injury in previously healthy persons who reported using e-cigarettes or vaping. The Centers for Disease Control and Prevention reported the precise source of the outbreak as currently unknown; however, the predominant use of prefilled tetrahydrocannabinol-containing cartridges among patients with lung injury associated with e-cigarette use suggested that these products played an important role. Device and products: Detailed patient interviews were conducted. Numerous products and brand names were identified by patients. Among the 86 interviewed patients, 75 (87%) reported using e-cigarette products containing tetrahydrocannabinol, the principal psychoactive component of cannabis, during the 3 months preceding illness; 61 (71%) reported using nicotine-containing products; 50 (58%) reported using both tetrahydrocannabinol- and nicotine-containing products. Twenty-five (29%) patients reported exclusive use of tetrahydrocannabinol-containing products, whereas 11 (13%) reported exclusive use of nicotine-containing products. In total 234 unique e-cigarette, or vaping, products labelled with 87 different brand names were reported. Nicotine-containing product users reported a mean of 1.3 different nicotine brands, and tetrahydrocannabinol containing product users reported a mean of 2.1 different tetrahydrocannabinol brands. Nearly all (96%) tetrahydrocannabinol -containing products reported were packaged, prefilled cartridges, and 89% were primarily acquired from informal sources (e.g., friends, family members, illicit dealers, or off the street). In contrast, 77% of nicotine-containing products were sold as prefilled cartridges, and 83% were obtained from commercial vendors.
Navon et al.[289] 2019	Harm	In the Morbidity and Mortality Weekly Report of the US Department of Health and Human Services and Centers for Disease Control and Prevention, first posted in November 2019, the authors reported on risk factors of e-cigarette, or vaping, products used by patients in Illinois. The Illinois Department of Public Health conducted an online public survey between September and October 2019 targeting e-cigarette, or vaping, product users in Illinois, examining whether e-cigarette, or vaping, product use behaviours differed between adult e-cigarette, or vaping, product use-associated lung injury patients and adults who used these products but did not develop lung injury. Among 4,631 survey respondents, 94% reported using any nicotine-containing e-cigarette, or vaping, products in the past 3 months; 21% had used any tetrahydrocannabinol-containing products; and 11% had used both tetrahydrocannabinol-containing products and nicotine-containing products. The prevalence of tetrahydrocannabinol-containing product use was highest among survey respondents aged 18–24 years (36%), and decreased with increasing age. E-cigarette, or vaping, product use behaviours of 66 e-cigarette, or vaping, product use-associated lung injury patients aged 18–44 years who were interviewed as part of the ongoing outbreak investigation were compared with a subset of 519 survey respondents aged 18–44 years who reported use of tetrahydrocannabinol-containing e-cigarette, or vaping, products. Compared with these survey respondents, product use-associated lung injury patients had higher odds of reporting exclusive use of tetrahydrocannabinol-containing products (AOR: 2.0; 95% CI: 1.1–3.6); frequent use (more than five times per day) of these products (AOR: 3.1; 95% CI: 1.6–6.0); and obtaining these products from informal sources, such as a dealer, off the street, or from a friend (AOR: 9.2; 95% CI: 2.2–39.4). The odds of using Dank Vapes, a class of largely counterfeit

	tetrahydrocannabinol-containing products, was also higher among e-cigarette, or vaping, product use-associated lung injury patients (AOR: 8.5; 95% CI: 3.8–19.0). Device and products: Any nicotine-containing products. Only nicotine-containing products. Any nicotine-containing product <1x/day§. Any nicotine-containing product >5x/day§. Any tetrahydrocannabinol-containing products. Only tetrahydrocannabinol-containing products. Any tetrahydrocannabinol-containing product <1x/day§. Any tetrahydrocannabinol-containing product >5x/day§. Dank Vapes*. Obtained any tetrahydrocannabinol-containing product informally**. Both tetrahydrocannabinol- and nicotine-containing products.

Appendix 3: Cross-sectional survey papers by adapted Academies of Sciences framework headings for e-cigarettes

Table 67: Cross-sectional surveys papers on dependence and abuse lability, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		Smoking reduction, smoking cessation and nicotine
Farsalinos et al.[202] 2013b	Benefit	The authors described the **nicotine levels used in order to achieve smoking cessation**, as well as the reported benefits, associated side effects, and estimation of e-cigarette dependence, compared with tobacco cigarette dependence. Age: 20 to 55 years. Sex: Most participants (84%) were male. Country: Greece Data source: Participants were recruited for research protocols evaluating the clinical effects of e-cigarette use, which were implemented in 2012 and early 2013 Population size: One hundred and thirteen vapers participate (32 hospital visitors and 81 members of consumers' Internet forum). Data collection period: 2012, 2013 E-cigarette, smoking and other related status: A significant proportion of the study sample consisted of formerly heavy smokers (smoking more than 20 cigarettes per day). Forty-eight of them (42%) quit smoking during the first month of using e-cigarette; 22 (19.8% of the whole group) quit on the first day. All participants achieved smoking abstinence by using second-generation (eGo-type batteries, 90.9%) or third-generation (variable voltage, often called "Mod") devices (9.1%). Thirty-five participants (31.5%) reported that they initiated e-cigarette use with a first-generation cigarette-like device. Outcomes: Smoking abstinence and dependency The authors concluded that nicotine levels appear to play an important role in achieving and maintaining smoking cessation in the group of motivated subjects studied. High-nicotine-containing liquids were used, but few mild and temporary side effects were reported. The authors concluded that regulatory proposals should consider the pragmatic use patterns of e-cigarettes, especially in consumers who have completely substituted tobacco cigarettes with e-cigarettes. Device and products: Subjects were included in the analysis irrespective of the type of e-cigarette devices or nicotine-level liquids they were using.[202]
Farsalinos et al[449] 2014a	Benefit	The authors described the characteristics, perceived **side effects, and benefits of e-cigarettes.** Age (median) years: 39. Sex: a significantly higher proportion were males Country: worldwide survey 74.7% from Europe, 20.7% from America, 1.8% from Asia, 1.1% from Australia, and 0.2% from Africa Data source: A questionnaire was developed and uploaded in an online survey tool (www.surveymonkey.com). The questionnaire was available in 10 languages (Czech, English, French, German, Greek, Hungarian, Italian, Polish, Russian, and Spanish). Population size: 19,441. Data collection period: April 2013 until July 2013

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		E-cigarette, smoking and other related status: former smokers and current smokers: current smokers 3682, former smokers 15,671, all e-cigarette users but 244 no longer current users Outcomes: characteristics and experiences of e-cigarette users and the differences between those who partially and completely substituted smoking with e-cigarette use They concluded that e-cigarettes are mostly used to avoid the harm associated with smoking. They noted that e-cigarettes can be effective even in highly dependent smokers, and that they are used as long-term substitutes for smoking. High levels of nicotine are used at initiation; subsequently, e-cigarette users try to reduce nicotine consumption, with only a small minority using non-nicotine liquids. Side effects are minor and health benefits are substantial, especially for those who completely substitute tobacco cigarettes with e-cigarettes. Device and products: E-cigarette device most often used: Cigarette-like, eGo batteries "Mods"; e-cigarette liquid use: prefilled cartomisers , ready-to-use liquids, do-it-yourself liquids; e-cigarette daily consumption mL liquid per day, nr of cartridges per day; Current nicotine levels in e-cigarette, and Nicotine levels at initiation of e-cigarette use
Etter et al.[203] 2015	Benefit	The authors reported on the **dependence level** in users of **e-cigarettes, nicotine gum, and tobacco cigarettes.** Age (mean) years: Former smokers 44.7, Daily e-cigarette users 40.9, Daily e-cigarette users 44.6, internet population 37.8 General population 40.1 Sex (males %): Former smokers 38.6, Daily e-cigarette users 68.9, Daily e-cigarette users 57.1, internet population 36.8 General population 58.4 Country: Respondence to the smoking cessation website Stop-tabac.ch Data source: Internet and mail surveys Population size: 4,781. Data collection period: October 2012 to October 2013 E-cigarette, smoking and other related status: 766 daily users of nicotine-containing e-cigarettes with 30 daily users of nicotine-free e-cigarettes; (b) 911 former smokers who used the e-cigarette daily with 451 former smokers who used the nicotine gum daily (but no e-cigarette); (c) 125 daily e-cigarette users who smoked daily (dual users) with two samples of daily smokers who did not use e-cigarettes (2206 enrolled on the Internet and 292 enrolled by mail from the general population of Geneva Outcomes: Dependence ratings They concluded that some e-cigarette users were dependent on nicotine-containing e-cigarettes, but that these products were less addictive than tobacco cigarettes. E-cigarettes may be as addictive as or less addictive than nicotine gums, which themselves are not very addictive.[203]. Device and products: Not reported
Baweja et al.[200] 2016	Benefit	The authors reported on the **experiences, satisfaction, opinions, and preferences of e-cigarette users.** Age: 30 to 50 years. Sex: 146 males. Country: 175/200 USA. Ethnicity: 177 white Data source: Online survey

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		Population size: 200 participants randomly selected from a sample of 1,177 persons who completed an online survey about their electronic cigarette preferences Data collection period: December 2012 to May 2014 E-cigarette, smoking and other related status: Cigarette smoking status - Past user (166) Current occasional user (13) Current daily user (21) Days Since quit Smoking (Past cigarette users only) 90–730, Quit smoking (166) Long before started using e-cigarettes (13) After started using e-cigarettes (153) History of other types of tobacco use Pipe smoker (43) Cigar smoker (80) Smokeless/chewing tobacco (69) Hookah user (49) Outcomes: Multiple see subsequent text. The sample was selected from a group of electronic cigarette users invited to complete an online survey aiming to improve understanding of the use of e-cigarettes, including the types of e-cigarettes being used, how frequently they are used and whether or not they are replacing other types of tobacco among e-cigarette users aged ≥18 years old. Participation in this study was voluntary and respondents could remain anonymous, although individuals who wished to volunteer for additional research on e-cigarettes were invited to enter their contact details at the end of the survey. The survey was administered, and responses were stored on REDCap (Research Electronic Data Capture). Information on a range of variables was gathered include information on: electronic cigarette use times per day (one ‘‘TIME’’ consists of around 15 puffs, or lasts around 10 minutes), number of models of e-cigarettes have been used prior to the current one, electronic cigarette contains button to press just prior to inhalation/puffing, type of liquid used in e-cigarette (Propylene glycol, Vegetable glycerine (VG), Both propylene glycol and VG). A 158-item questionnaire was administered with questions on the use of the electronic cigarette, differences in use between e-cigarettes and conventional combustible tobacco cigarettes, important characteristics of e-cigarettes and effects associated with e-cigarette use. In this latter area, effects associated with e-cigarettes use 14 themes were identified. Here, approximately one-fourth of responses were related to experiencing no undesirable effects (25 comments, ‘‘No negative effects, they have all been positive’’). The most common negative effects were: symptoms related to dehydration including dry mouth, chapped lips and bad breath (25 comments, ‘‘Dry mouth occurred more when I first started using the e-cigarette and was every time I used it’’); worsening respiratory symptoms (10 comments, ‘‘Exacerbation of asthma symptoms’’); side effects possibly related to nicotine effects (8 comments, ‘‘headaches are from high nicotine’’); followed by throat and nasal irritations (8 comments), transient headache (6 comments), increased heart rate (5 comments). A number of other symptoms were mentioned by only one respondent. Of the participants who reported undesirable effects, 13 spontaneously mentioned the transient nature of the undesirable effects (‘‘In the first few months when I was trying all those new kinds, I did have dry mouth & other symptoms but not with what I use now’’). The physical health related outcome on which data were gathered included the experienced effects as a result of e-cigarettes (quite often/once a week): dry mouth, dry cough, throat irritation. There were 15 positive themes identified from responses. The most frequently cited positive aspects of e-cigarette use were: assisted in smoking cessation and reduced cigarette consumption (81 comments, ‘‘As far as Nicotine Replacement Devices go, e-cigarettes are fantastic. Both my wife and I quit smoking after 15 years’’); beneficial effect on health (71

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		comments, ‘‘My blood pressure has stabilized and have, under doctors [sic] orders, quit taking some of my medications for it’’); improved breathing, decreased cough, fewer sore throats (70 comments, ‘‘Breathing is easier. No hacking cough at any time of the day’’); safe way to use nicotine (42 comments, ‘‘I’m still on nicotine, but much less. I’m avoiding close to 4000 chemicals in a conventional combustible tobacco cigarette’’); followed by pleasure of inhaling and smoking-related actions (34 comments); comparatively less toxic than smoking tobacco (33 comments); improvement in sense of smell and taste (32 comments); less expensive than cigarettes (28 comments); feasibility to use e-cigarettes (23 comments); similar gestures or action of smoking cigarette (21 comments); not associated with unpleasant odours and ash or dirt (21 comments); taste and variety of flavours (12 comments); safe for others or bystander with no second hand smoke (10 comments); helped relieve the craving for tobacco (10 comments), and improvement in dental health (4 comments). They concluded that experienced e-cigarette users stated that initiating e-cigarette use helped them to quit or reduce their conventional smoking, which they believed reduced their health risks. In comparison to cigarette smoking, e-cigarette users reported using their e-cigarette more times per day, but with fewer puffs than on conventional combustible tobacco cigarettes at each use time. E-cigarette users acknowledged that more research is needed in order to understand the safety and long-term effects of use. Finally, the e-cigarette users mentioned dry mouth as a common side effect and they also noted common problems with the reliability of e-cigarettes.[200] Device and products: Most e-cigarette users had tried at least three different models prior to the one they were using currently. Almost half of the users spent more than 50 U.S. dollars on their current e-cigarette with a weekly maintenance cost of approximately 10 U.S. dollars. The most frequently used e-cigarette contained a button to press prior to inhalation/puffing (79.5%), had a tank to hold the liquid (58.5%), and used both propylene glycol and vegetable glycerine (68.8%)[200]
Comiford et al.[205] 2018	Harm	The authors reported on the relationship between **e-cigarette use and smoking-related measures** (salivary cotinine levels) among American Indians who smoked. Age: Age groupings were categorized as years 18-44 and 45+. Sex: 145 males, 230 females Country: USA. Ethnicity: Cherokee citizens reside in the area under tribal administration Data source: Research staff recruited study participants from a high-traffic waiting area within the W.W. Hastings primary care outpatient facility in Tahlequah, Oklahoma. Population size: 375. Data collection period: Not reported E-cigarette, smoking and other related status: Status of e-cigarette use was assessed with the following questions: “Have you ever vaped or used an e-cig, even one or 2 times?” and, “On how many of the past 30 days did you use an e-cigarette or vape even one or 2 times?” Individuals were considered current e-cigarette users if they reported e-cigarette use within the past 30 days. Individuals were considered past e-cigarette users if they ever used e-cigarettes but did not use within the past 30 days. Individuals were considered never e-cigarette users if they had never used e-cigarettes, even one or 2 times. The sample consider of 375 smokers of which 137 never used an e-cigarette, 178 were past users of e-cigarettes and 60 were

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		current e-cigarette users. Other tobacco use (current, past, or never) was based on use of smokeless tobacco, cigars, cigarillos, filtered cigars, hookahs, or dissolvable tobacco. Never use was defined as having never tried any of the identified tobacco products. Past use was defined as either having tried or yearly use of any of the identified tobacco products. Current use was defined as daily, weekly, or monthly use of any of these or other tobacco products. Individuals were considered current e-cigarette users if they reported e-cigarette use within the past 30 days. Individuals were considered past e-cigarette users if they ever used e-cigarettes but did not use within the past 30 days. Individuals were considered never e-cigarette users if they had never used e-cigarettes, even one or 2 times. Outcomes: Salivary cotinine levels and measures of intention to quit smoking. More than 63% of the study population reported use of e-cigarettes either currently or in the past. The results did not suggest that e-cigarette use is associated with a reduction of cigarette consumption to less than one pack per day. Current use of cigarettes and e-cigarettes was associated with quit attempts in the past 12 months and a self-reported likelihood of future tobacco cessation, and that this may be an indication that e-cigarette use may signify a greater interest in smoking cessation. However, e-cigarette use was not associated with confidence to quit in the next month, cigarette packs smoked per day, or salivary cotinine levels.[205] Device and products: Not reported.
Johnson et al.[206] 2018	Harm	The authors reported on the relationship between characteristics of **e-cigarette usage and Fagerström Test for Nicotine Dependence outcome scores**, specifically scores on nicotine dependence. Age: males were 31 years old (range 18–68, standard deviation (SD) = 11.1) and females were 35 years old (range 18–56, SD = 11.5) Sex: 72% were male and 28% female. Country: USA. Data source: A convenient sample of e-cigarette users attending a large South-eastern e-cigarette convention in Fall 2015. Surveys were placed on a table manned by a researcher in the convention centre entrance lobby. Subjects were able to approach the table and receive a paper survey to complete. Population size: 131. Data collection period: October 2015. E-cigarette, smoking and other related status: Low dependence, low to moderate dependence, moderate dependence, high dependence Outcomes: All questions from the Fagerstrom Test for Nicotine Dependence were included as well as select questions from the Penn State Electronic Cigarette Dependence Index. In total 25 questions were used to derived measures of addictive and behavioural characteristics and nicotine dependence rankings. The authors concluded that e-cigarette users can have higher average nicotine dependence levels than conventional combustible tobacco cigarette users. They noted that the length of e-cigarette use (<1 year versus >1 year) and the level of nicotine used in e-cigarette liquid (none versus any level of nicotine) were significantly associated with the Fagerström Test for Nicotine Dependence scores. They also noted that those who used e-cigarette fluid with no nicotine had lower scores than those who used fluids that contained nicotine.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		Device and products: This study surveyed 131 adult attendees at the "Orlando Vape Convention" on October 17, 2015. An estimated 1000 people attended to socialize and purchase e-cigarette liquids and supplies from approximately 40 vendors. An e-cigarette convention was chosen as the venue because it attracted many intense e-cigarette users over a short amount of time. Only current e-cigarette users were eligible to complete the survey. However, information on the type of device used by participants was not reported.[206]
Piper *et al.*[204] 2018	Harmful, but less harmful than tobacco cigarettes	The authors reported on the relationship between completed **baseline assessments of demographics, tobacco use, and dependence**. They also provided details of breath samples for carbon monoxide (CO) assay and urine samples for cotinine, 3-hydroxycotinine (3HC), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL, a carcinogen) assays. Age in years: (Mean [SD]) Total 40.4 (14.1), Smokers 42.6 (14.4), Dual user 39.0 (13.8). Sex: Slightly more than half were men (53.1%). Country USA Data source: Participants were recruited from the greater Madison and Milwaukee, WI areas via television and social media (e.g., Facebook) advertisements seeking adults who smoke or use e-cigarettes to participate in a study that tracks tobacco use. Interested callers completed a telephone screen, and eligible participants attended an initial study visit where they learned about the study and provided written informed consent. The authors initially set a minimum of 5 cigarettes/day for dual users, but this created difficulty with recruitment (i.e., 28% [57 of the 560] of the e-cigarette users were disqualified for smoking fewer than 5 cigarettes/day). Therefore, approximately 6 months into the 2-year recruitment the authors changed the dual use criteria to require that dual users merely needed to have smoked daily for the last 3 months. The authors thus determined this to be an examination of an observational cohort (smokers, n = 166, ≥5 cigarettes/day for 6 months and no e-cigarette use in 3 months; dual users, n = 256, smoked daily for 3 months and used e-cigarettes at least once/week for the past 3 months). This longitudinal observational cohort study explores use patterns and health indices over a 2-year period. The data reported here are from the baseline assessments. Population size: Total N = 422, Smokers (n = 166), Dual users (n = 256) Data collection period: Year not reported E-cigarette, smoking and other related status: compared smokers and dual users on indices of dependence and smoke exposure, including biomarkers Outcomes: baseline assessments of demographics, tobacco use, and dependence. Breath samples for carbon monoxide (CO) assay and urine samples for cotinine, 3-hydroxycotinine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) assays. Smoking dependence measures: Cigarettes/day, Expired carbon monoxide (CO), Fagerstrom Test for Cigarette Dependence (FTCD), Smoke in first 30 minutes, Wisconsin Inventory of Smoking Dependence Motives Primary Dependence Motives (WISDM PDM), Wisconsin Inventory of Smoking Dependence Motives Secondary Dependence Motives (WISDM SDM), WISMD total. The authors concluded that dual users were more likely to be white, be younger, have more than a high school education, and have a psychiatric history. Dual users also smoked significantly fewer cigarettes and had lower levels of NNAL (a carcinogen), but they did not differ from exclusive smokers in terms of carbon monoxide or cotinine levels, suggesting that they supplemented their nicotine intake via e-cigarettes[204]

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		Device and products: Among the dual users, the most common type of device used was a refillable tank (65.3%), followed by replaceable cartridges (19.2%), and disposables (11.4%). The most commonly used e-liquid flavours were fruit (42.3%) and menthol (19.9%); 9% had no preference, 6.6% preferred candy flavours, and 6.6% used tobacco flavoured liquid. The preferred nicotine content in the e-liquid (listed in order of prevalence) was high nicotine (18–24 mg; 27.8%), very low nicotine (1–6 mg; 26.9%), low-to-medium nicotine (7–12 mg; 23.3%), medium-to-high nicotine (13–17 mg; 14.8%), very high nicotine (>24 mg; 4.5%), and no nicotine (2.7%).
Boykan et al.[207] 2019	Harm	The authors reported on differences in urinary cotinine levels in **pod versus non-pod** e-cigarette users. In addition, they assessed **dependence levels** in a subset of the original population. Age: 12-21 year. Sex: Not reported. County: USA Data source: Stony Brook Children outpatient office attendees Population size: 92 (of which 42 were considered in the secondary analysis of the following groups: past week pod users n=21, past week e-cigarette users who did not use pods n=27 (combustible pod users were excluded) Data collection period: April 2017 to April 2018 E-cigarette, smoking and other related status: reported as past week pod users n=21, or past week e-cigarette users who did not use pods n=27 and 2.9% (n = 18) were past-week tobacco smokers. Outcomes: early onset of nicotine addiction The authors concluded that adolescents who used pod products showed more signs of nicotine dependence than non-pod users. Positive responses to dependence questions were reflected in higher urinary cotinine levels[207] Device and products: Not reported
Jankowski et al.[208] 2019	Harm	The authors reported on levels of **pain severity and anxiety sensitivity interplay among exclusive e-cigarette users and dual e-cigarette and conventional combustible tobacco cigarette users.** Age (mean) (SD) years: 22.4 (2.2). Sex:60% males, 40% females. Country: Poland Data source: survey-based and multicentred international project, the Young People E-Smoking Study Population size: 93, 39 exclusive e-cigarette users and 54 dual users Data collection period: January and March 2018 E-cigarette, smoking and other related status: exclusive e-cigarette users and dual users Outcomes: nicotine dependence levels The authors concluded that the findings suggest that there needs to be further study of anxiety sensitivity and pain severity in the context of e-cigarette use, as there may be a benefit to screening for and clinically addressing these factors in order to help offset e-cigarette use..[208] Device and products: Not specifically reported. But the following information was provided: nicotine content in the e-liquid, e-liquid consumption, type of e-liquid used, and the number of e-cigarettes used, did not differ significantly between e-cigarette users and dual users. Users of e-cigarettes consumed an average of 4.2 mL of e-liquid per day, with the most frequently chosen e-liquid being that containing 6 mg of nicotine in 1

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		mL of e-liquid. None of the subjects used nicotine free e-liquids. The study population was dominated by individuals who prepared e-liquids themselves. Over half of the e-cigarette users of exclusive e-cigarette users and dual users; had chosen devices that allow technical modifications of the e-cigarette such as voltage, power, and resistance of the heater.[208]
		Mental health
Bandiera et al.[211] 2016	Harm	The authors reported on the relationship between **tobacco and nicotine product use and depressive symptoms.** Age: 18 to 29 years. Participants were required to be 18–26 years old if they were a lifetime non-tobacco user or 18–29 years old if they were a lifetime tobacco user Sex: 63.8% were female. Country: USA Data source: convenience sample of college students in 24 colleges and universities in Texas Population size: 5,438. Data collection period: November 2014 to February 2015. E-cigarette, smoking and other related status: Lifetime tobacco use was defined by having ever smoked at least 100 cigarettes, or at least 20 cigars, or having ever used smokeless/spit/chewing tobacco at least 20 times. Use of five types of tobacco/nicotine products were examined in the study, current or past 30-day use of cigarettes, smokeless/snus tobacco, large cigars/cigarillos/little cigars, hookah, and e-cigarettes. Current use of cigarettes, smokeless tobacco, and hookah were assessed with the questions “During the past 30 days, on how many days did you smoke/use____?” Current use of large cigars/cigarillos/little cigars and hookah were assessed with questions “During the past 30 days, how many days did you smoke as intended (i.e. with tobacco)?” Current use of e-cigarettes was assessed with the question “During the past 30 days, have you used any ENDS product (i.e., an e-cigarette, vape pen, or e-hookah), even one or two puffs, as intended (i.e. with nicotine cartridges and/or e-liquid/e-juice)?” Outcomes: Depressive symptoms were assessed with the 10-item short-form Centre for Epidemiologic Studies Depression 10 Scale (CES-D 10). Specifically, low depressive symptoms = CES-D score > 10; High depressive symptoms = CES-D score ≥ 10 The authors reported that e-cigarettes were the only alternative tobacco product that were uniquely associated with depressive symptoms, and that the association was significant even after controlling for current cigarette use, sociodemographic characteristics, and current use of three other three alternative tobacco products tested.[211] Device and products: Not reported
Bianco et al.[209] 2019	Harm	The authors reported on the **rates of e-cigarette use among adults with a chronic mental illness** (classified as depression, anxiety, emotional disorder, or ADD, bipolar disorder, schizophrenia, other disorders). Age: 50.77 (SD=18.61; range 18–85). Sex: 54.6% female. Country: USA. Ethnicity 80.3% white. Data source: National Health Interview Survey Population size: 33,028. Data collection period: 2016

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		E-cigarette, smoking and other related status: The majority of the sample did not have a chronic mental illness (97.1%, n=32,081), 2.7% (n=886) had chronic depression, anxiety, or an emotional problem, and 0.2% (n=61) had chronic ADD, bipolar, schizophrenia, or other disorder. Weighted percentages found 15.1% of the total sample tried an e-cigarette at least once and 3.1% were current e-cigarette users. Outcomes: Chronic mental illness (classified as depression, anxiety, emotional disorder, or attention deficit disorder (ADD), bipolar, schizophrenia, other disorder) The authors' paper included the following findings: approximately 14% of the adult population in the USA has tried an e-cigarette, or is trying an e-cigarette. Previous trial of an e-cigarette is more likely in a person with depression, anxiety, or an emotional problem (odds ratio (OR): 2.84). Trying an e-cigarette is more likely in a person with ADD, bipolar disorder, schizophrenia, or other disorder (OR: 2.47). Regular e-cigarette use is more likely in a person with depression, anxiety, or an emotional problem (OR: 2.69). Regular e-cigarette use is more likely in a person with ADD, bipolar disorder, schizophrenia, or other disorder (OR: 3.02). However, as the temporary path of mental health diagnosis and e-cigarette uptake was not specified, the reported relationship must be viewed as cross-sectional in nature. The authors concluded that logistic regressions suggested that having a chronic mental illness significantly increases the likelihood of both trying an e-cigarette and being an e-cigarette user.[209] Device and products: Not reported
Chadi et al.[210] 2019	Harm	The authors reported on the relationship between **e-cigarette and marijuana use and depressive symptoms and suicidality** in a large sample of high school students. Age: high school students. Sex: 51.3% were female. Country: USA, Ethnicity: half of the sample participants (26,821) were white. Data source: Youth Risk Behaviour Survey Population size: 26,821 Data collection period: 2015 and 2017 E-cigarette, smoking and other related status: Four exposure groups for current e-cigarette and marijuana use: no use, e-cigarette-only use, marijuana-only use, and dual use. E-cigarette-only use was reported by 9.1% of participants, marijuana-only use in 9.7%, and dual e-cigarette/marijuana use in 10.2%. No Use (n=19047) E-Cigarettes Only (n=2431) Marijuana Only n=259 Dual Use n=2749 Outcomes: Responses to the following questions: During the past 12 months, did you ever seriously consider attempting suicide? Yes, no, unknown and During the past 12 months, did you ever feel so sad or hopeless almost every day for 2 weeks or more in a row that you stopped doing some usual activities? Answers were assessed to establish is participants had seriously considered suicide in the past 12 months, or endorsed symptoms of major depression for a 2-week period in the past 12 months Almost one-third of participants (30.7%) reported experiencing depressive symptoms for more than 2 weeks and 17.3% reported seriously considering attempting suicide in the past year. E-cigarette-only use (vs no use) was associated with higher odds of reporting seriously considering attempting suicide in the past year (adjusted odds ratio [AOR]: 1.23, 95% CI 1.03–1.47),

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		which was also observed with marijuana-only use (vs no use) (AOR: 1.25, 95%CI 1.04–1.50), and dual use (vs no use) (AOR: 1.28, 95% CI 1.06–1.54), Similarly, e-cigarette-only use (vs no use) was associated with higher odds of reporting depressive symptoms (AOR: 1.37, 95% CI 1.19–1.57), which was also observed with marijuana-only use (AOR: 1.49, 95% CI 1.27–1.75) and dual use (AOR: 1.62, 95%CI: 1.39–1.88). Finally, there was a non-significant trend towards higher odds of reporting suicidality and depressive symptoms among participants with dual e-cigarette and marijuana use vs single e-cigarette or marijuana use. The authors stated that adolescents who admitted e-cigarette-only use, marijuana-only use, or dual e-cigarette and marijuana use had poorer mental health outcomes compared to those who denied use, when adjusting for demographic factors, use of other substances, and other relevant confounders. The association between depression and use of e-cigarettes has previously been reported in a nationally representative sample of adolescents, but the association between e-cigarette use and suicidality has not. The authors observed an increased likelihood of depressive symptoms and suicidal ideation in all three investigated substance use categories (e-cigarette-only, marijuana-only, and dual e-cigarette/marijuana use).[210] Device and products: The study sample included only participants with complete information for exposure to e-cigarettes and marijuana (89.5% of survey respondents). Participants were divided into 4 exposure groups for current e-cigarette and marijuana use: no use, e-cigarette-only use, marijuana-only use, and dual use. Current use was defined as use of the specified substance at least once in the past 30 days[210]
Lee *et al.*[213] 2019a	Harm	The authors reported on the association of **depression and suicidality with electronic and conventional combustible tobacco cigarette use** in South Korean adolescents. Age: 13–18 years old. Sex: Not reported. Mixed. Country: South Korea Data source: Korean Youth Risk Behaviour Web-based Survey Population size: 62,276. Data collection period: April 2017 E-cigarette, smoking and other related status: Participants were categorized into four groups: current non-use, conventional-cigarette-only use, e-cigarette only use, and dual use. Participants were assessed by asking “Have you ever used cigarettes in the past 30 days?” (yes/no) and “Have you ever used e-cigarettes in the past 30 days?” (yes/no). Outcomes: This web-based survey comprised 123 questions and 15 areas of health-related behaviours, including smoking behaviour and mental health. A multivariate logistic regression was performed to assess the association of depression and suicidality with electronic and conventional cigarette use. There were significant differences between tobacco cigarette and e-cigarette users: dual users had a higher prevalence of depression and suicidality for both lifetime and current use; e-cigarette-only users had higher levels of depression and suicidality than non-users; and female adolescents who were conventional-cigarette-only users, e-cigarette-only users, or dual users had a higher prevalence of depression and suicidality than male adolescents in those user categories. The authors concluded that the findings suggest an urgent need for evaluation of, and intervention in, e-cigarette use by health professionals providing smoking cessation programmes for adolescents.[213] Device and products: Not reported

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
Kim[212] 2019	Harm	The author investigated the association of the use of e-**cigarettes with suicidal behaviour**s in adolescents Age: 13 to 18 years. Sex: 4,380 males, 1,024 females Country: South Korea Data source: Korean Youth Risk Behaviour Web-Based Survey Population size: 5405. Data collection period: 2016 E-cigarette, smoking and other related status: E-cigarette use was assessed by the item, 'How many days did you use e-cigarettes in the past 30 days?' Response options were 'None,' '1–2 days,' '3–5 days,' '6–9 days,' '10–19 days,' '20–29 days' and 'Every day.' This study categorized e-cigarette users into two categories: '0 days in the past 30 days,' which included those who answered 'None,' and '1–30 days in the past 30 days,' which included those who answered '1–2 days,' '3–5 days,' '6–9 days,' '10–19 days,' '20–29 days' and 'Every day.' Outcomes: suicidal ideation, suicidal attempts and serious suicidal attempts The author concluded suicidal behaviours are significantly higher among current adolescent e-cigarette smokers than adolescents who have not used an e-cigarette in the past 30 days[212] Device and products: Not reported
Zvolensky et al.[214] 2019	Harm	The authors reported-on levels of **pain severity and anxiety sensitivity interplay among exclusive and dual e-cigarette user** Age mean (SD) years = 36.8 (10.6). Sex: 126 males, 193 females Country: USA. Ethnicity: White (78.1%) individuals, followed by 14.4% Black/African American, 9.7% Hispanic, 3.4% Asian, 2.2% other, and 1.9% Native American/Alaska Native Data source: Participants were recruited nationally via Qualtrics Inc. Interested participants were screened for eligibility and directed to the online, anonymous survey. Population size: 319. Data collection period: Not reported E-cigarette, smoking and other related status: e-cigarette users: The study included 319 current e-cigarette users Outcomes: anxiety sensitivity and pain severity. The interaction between anxiety sensitivity and pain severity was significantly related to increased e-cigarette dependence, perceived risks of e-cigarette use, and perceived benefits of e-cigarette use. The form of the significant interaction indicated that participants reporting co-occurring higher levels of anxiety sensitivity and pain severity evinced greater e-cigarette dependence, perceived risks of e-cigarette use, and perceived benefits of e-cigarette use. The authors concluded that the findings suggest there needs to be further study of anxiety sensitivity and pain severity in the context of e-cigarette use, as there may be benefit to screening for and clinically addressing these factors to help offset e-cigarette use[214] Device and products: Not reported
		Body weight

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
Lanza et al.[215] 2017	Harm	The authors reported on the relationship **between e-cigarette and conventional combustible tobacco cigarette use and higher weight status (obesity).** Age: The average age of participants was 21.3 years ± 2.6 (median = 21.0 years) Sex: 59.1% (56.2%) female. Country: USA, Ethnicity: 36.9% (39.0%) Hispanic/Latino, 26.3% (23.4%) Asian/Pacific Islander, 17.9% (18.7%) Caucasian/White, 4.9% (3.8%) African American/Black, 5.1% (4.8%) Multiracial; 2.1% (3.6%) other, 0.2% (0.2%) Native American, and 6.6% declined to respond Data source: convenience sample of 452 undergraduates attending a California State University Population size: 452. Data collection period: 2015-2016 E-cigarette, smoking and other related status: Participants were then asked questions related to cigarette smoking and electronic tobacco use: (1) “Have you ever smoked a cigarette?” (1 = yes, 0 = no); (2) “In the past month, have you smoked cigarettes regularly (at least 5 times in the last 30-day period)?” (1 = yes, 0 = no); and (3) “Have you ever smoked cigarettes regularly (at least 5 times in a 30-day period)?” which was used to create a former cigarette smoker variable (1 = yes, 0 = no) by comparing responses from question 3 to question 2. Because there was no available validated questionnaire on young adult electronic tobacco use at the time of survey development and implementation, questions on electronic tobacco use were developed for this specific study. Two questions on prevalence included: (1) “Have you ever tried an electronic tobacco product (like e-cigarettes, vaporizers, e-hookahs)?” (1 = yes, 0 = no); and (2) “Would you consider yourself a regular user of any electronic tobacco product, like e-cigarettes, vaporizers, or e-hookahs?” (1 = yes, 0 = no). Almost 40% (39.8%) of the sample had engaged in electronic tobacco use, and 5% self-identified as a regular electronic tobacco user. Outcomes: weight status as a correlate of substance use patterns reflecting electronic tobacco use. Data on 118 questions pertaining to electronic tobacco use, alcohol use, cigarette smoking, nutrition and physical activity, and psychosocial adjustment. Participants self-reported height and weight, which was used to calculate body mass index (BMI; weight(lbs)/[height(in)2 x 703). Those with a BMI score > 30 were identified as obese (1 = obese, 0 = non-obese). indicators of weight status, obesity and deviation from the group BMI norm, were generally associated with membership in the Cigarette/Electronic Tobacco class. Obese participants had a higher likelihood of belonging to the Cigarette/Electronic Tobacco class compared to the High Substance Use (β =1.48, OR = 4.40, p < .05) and Risky Alcohol Use (β =1.94, OR = 6.97, p < .05) classes; however, higher likelihood of being classified into the Cigarette/Electronic Tobacco class compared to the Low Substance Use class was only marginally significant (β =1.29, OR = 3.63, p = .07). Greater deviation from the group BMI norm significantly predicted higher likelihood of belonging to the Cigarette/Electronic Tobacco class compared to the Low Substance Use (β =.11, OR = 1.11, p <.05) and High Substance Use (β =.11, OR = 1.12, p < .05) classes; but a higher likelihood of belonging to the Cigarette/Electronic Tobacco class compared to the Risky Alcohol Use class was only marginally significant (β =.11, OR = 1.11, p = .06). Both obesity status and greater deviation from one’s group body mass index (BMI) norm were associated with a higher likelihood of belonging to the Cigarette/Electronic Tobacco Use class

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		The authors concluded that the relationship between obesity and cigarette smoking may extend to e-cigarette use among young adults.[215] Device and products: Not reported
Morean et al.[216] 2019	Harm	The authors reported on the relationship between **use of flavoured e-cigarettes and e-liquids with appetite control and weight loss.** The authors concluded that a subset of adolescents reported using flavoured e-liquids for weight-related reasons. These adolescents reported vaping more frequently than their counterparts, raising concerns about increased nicotine exposure. Research is needed in order to understand where adolescents learn about weight-motivated vaping (e.g. friends, social media) and whether weight-related motives promote e-cigarette initiation among e-cigarette-naive individuals or continued/escalating use among current users. Age mean (SD) (range) years: 16.3 (1.2) (13 to 19). Sex: 49.4% males, 50.6% females. Country: USA Data source: school-based survey Population size: 529. Data collection period: Spring 2017 E-cigarette, smoking and other related status: students with positive answers to the following questions: approximately how many days out of the past 30 days did you vape an e-cigarette/smoke a cigarette?" (0–30 days). Participants who vaped/smoked on ≥1 day in the past 30 days were considered past-month e-cigarette users and/or smokers, respectively Outcomes: assessment of aadolescent e-cigarette users (past 30-days) who reported vaping flavoured e-liquids for appetite control and weight loss. The authors concluded that a subset of adolescents reported using flavoured e-liquids for weight-related reasons. These adolescents reported vaping more frequently than their counterparts, raising concerns about increased nicotine exposure. Research is needed in order to understand where adolescents learn about weight-motivated vaping (e.g. friends, social media) and whether weight-related motives promote e-cigarette initiation among e-cigarette-naive individuals or continued/escalating use among current users.[216] Device and products: Information on whether participants had "vaped e-cigarettes with nicotine in the past 30 days" (no/yes), "which flavours [they had] used in the past 30 days" (response options: tobacco, menthol, mint, fruit, candy, vanilla, alcohol, coffee, spice, other, and I don't know), and "Why do you use flavoured e-liquids?" (select all that apply from they taste better than regular cigarettes, they help me to cut down on smoking regular cigarettes, they help me to quit smoking, they freshen my breath, they provide a throat hit, they taste good, they help me control my appetite, they help me lose weight, and other (write-in)
		Sleep pattern
Boddu et al.[217] 2019	Harm	The authors reported on the **effects of e-cigarettes on sleep.** Age: 30.2 (12.3). Sex: 134 males, 139 females Country: 20 USA states, 12 countries (not named) Data source: online social media advertisement Population size: 274. Data collection period: Not reported

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		E-cigarette, smoking and other related status: Non-smokers (n=126) conventional cigarette users (n=25) e-cigarettes users (n=79) Dual users (n=44) Outcomes: Sleep disturbance associated with e-cigarette assessed by clinically validated sleep and cough questionnaires – Pittsburgh Sleep Quality Index and Leicester Cough Questionnaire assessment of the impact of cough severity on health-related quality of life, across physical, psychological and social domains) The authors found that dual use of e-cigarettes with conventional tobacco has the highest risk for causing sleep disruption. They concluded that mechanistically, this finding is logical if nicotine is the causal agent of sleep disruption, as dual users are more likely to consume greater concentrations of nicotine than either smokers or vapers. This notion may reveal the underlying mechanism for poorer sleep quality and for increased odds and severity of cough in dual users.dual.[217] Device and products: Not reported but the authors noted that JUUL™, which contains higher concentration of nicotine compared to conventional tobacco cigarettes (up to 60mg/mL)is used by >50% of current e-cigarettes vapers since 2017[217]
Brett et al.[218] 2019	Harm	The authors reported on the relationship between **e-cigarette use and sleep health** in young adults. Age:19.7 (2.5). Sex: 44% males, 66% females. Country: USA Data source: Undergraduates from a midwestern university self-selected into the study through the university online research recruitment system Population size: 1,664 college students. Data collection period: Not reported E-cigarette, smoking and other related status: Nine hundred and eighty-four participants (59%) reported never using an e-cigarette. Five hundred and forty-six participants (33%) reported ever trying an e-cigarette, and 134 (8%) reported e-cigarette use at least once each month. Outcomes: Questionnaires assessed demographic information, sleep health (assessed using the Pittsburgh Sleep Quality Index) and e-cigarette use status and patterns. The authors concluded that current combustible and e-cigarette users reported significantly more sleep difficulties than never users. E-cigarette users reported greater use of sleep medication than combustible cigarette users.[218] Device and products: Not reported [218]
Riehm et al.[219] 2019	Harm	The authors reported on the relationship between **e-cigarette use and sleep-related complaints** Age: 12 to 17. Sex: 4,914 males, 4,674 females, Country: USA Ethnicity: White only, Black only, other [American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, and Pacific Islanders) Data source: Population Assessment of Tobacco and Health Study, a nationally representative cohort Population size: 9,588. Data collection period: 2013 to 2015 E-cigarette, smoking and other related status: Participants were grouped in four mutually exclusive exposure categories based on their self-reported

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		past-year e-cigarette or combusted cigarette use at Wave 2: 1) exclusive e-cigarette use; 2) exclusive combusted cigarette use; 3) dual-product use; or 4) no use of either product. E-cigarette use was assessed by first asking adolescents "Which of the following electronic nicotine products have you ever used?" and presenting a list of products. Those who selected "E-cigarette (including vape pens and personal vaporizers)" were then asked, "When was the last time you used an e-cigarette, even one or two times?" Adolescents were considered to have used e-cigarettes if they selected a response that fell within the past year. Combustion cigarette use was assessed by asking "In the past 12 months, have you smoked a cigarette, even one or two puffs?" Adolescents were categorized as dual-product users if criteria for past-year use were met for both e-cigarettes and combusted cigarettes. Outcomes: adolescents who reported past-year e-cigarette and dual-product use had 29% and 57% higher odds of reporting sleep-related complaints, respectively, compared to no use of either product The authors concluded e-cigarette and dual-product use are significantly associated with greater odds of reporting sleep-related complaints among adolescents Device and products: Respondence were asked the following e-cigarette device related questions: For lifetime e-cigarette use (yes/no), adolescents were considered lifetime users if they responded "yes" to the question, "Have you ever used an e-cigarette, such as NJOY, Blu, or Smoking Everywhere, even one or two times?" For lifetime combusted cigarette use, adolescents were considered lifetime users if they responded "yes" to the question, "Have you ever tried cigarette smoking, even one or two puffs?". Have you ever used marijuana, hash, THC, grass, pot or weed?" or if they responded "yes" to the question, "Have you ever smoked part or all of a cigar, cigarillo or filtered cigar with marijuana in it?"[219]
		Perceived health
Lequy et al.[220] 2019	Harm	The authors reported on **perceived health** and its association **with current use of e-cigarettes** in current and former smokers. The authors concluded that the findings suggest that the unhealthier current and former smokers felt, the more they tended to currently use e-cigarettes. Authors reported on the **perceived health** and its association **with current use of e-cigarettes** in current and former vapers. Age: 18–69 years at baseline Current smokers – never n=4,805, current n=1,010. Former smokers - never n=11,986, current n=499 Sex: 8,778 males. County: France Data source: participants included in the French CONSTANCES cohort (a large general-purpose national population-based cohort) Population size: 18,300 ever tobacco smokers with data on their e-cigarette use Data collection period: 2015 to 2017 E-cigarette, smoking and other related status: Assessment of e-cigarette use as follows: "Have you ever smoked an electronic cigarette?" We defined participants answering yes as ever e-cigarette users. Among them, we distinguished between "Current e-cigarette user" and "Former e-cigarette user" through the following 2 questions: "Are you currently using disposable e-cigarettes?" or "Are you currently using refillable e-cigarettes?" Those

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers dependence and abuse liability
		who responded yes to at least one of these questions were classified as "Current e-cigarette user." Since we had no data about how many and how long former users had used e-cigarettes or why they had stopped, we excluded former e-cigarette users. Outcomes: global and respiratory perceived health. Specifically, answers to the following questions "How do you describe your general health?" and Any self-reported personal history of respiratory disease (at least 1 positive answer to asthma, chronic obstructive pulmonary disease, or emphysema) and the existence of an obstructive syndrome measured by spirometry at a screening health centre (defined as the ratio of forced expiratory volume in 1 second to forced vital capacity, or an forced expiratory volume in 1 second/forced vital capacity ratio < 0.7). The authors concluded that the findings suggest that the unhealthier current and former smokers felt, the more they tended to currently use e-cigarettes. Authors reported on the **perceived health** and its association **with current use of e-cigarettes** in current and former vapers.[220] Device and products: Not reported

Table 68: Cross-sectional surveys papers on cardiovascular disease, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cardiovascular disease
Boas et al.[221] 2017	Harm, but less harm than tobacco cigarettes	The authors reported on the relationship between **electronic and tobacco cigarettes** and the inflammatory signalling network underlying **acute cardiac ischaemia** (the Splenocardiac Axis). Age: 21 to 45 years. Sex: 20 males, 7 females. Country: USA. Ethnicity: African American n=1, Asian n=4, Hispanic n=3, White (non-Hispanic) n=19 Data source: healthy habitual tobacco cigarette smokers or habitual e-cigarette users (not dual users) who had used tobacco cigarettes or e-cigarettes, respectively, most days for a minimum of 1 year, in whom plasma cotinine levels were elevated, were eligible for the study if they met the study criteria: no known health problems, nonobese (≤30 kg/m2 BMI), not taking prescription medications except oral contraceptive pills, alcoholic intake ≤2 drinks per day and no illicit drug use, not exposed to second-hand smoke, or using licensed nicotine replacement therapies. Population size: 31. Data collection period: Not reported E-cigarette, smoking and other related status: 10 habitual tobacco cigarette users, 11 habitual e-cigarette users, and 10 healthy control subjects. Nine in each group were included in the final analysis Outcomes: F-flurorodeoxyglucose positron emission tomography/computer tomography (FDG-PET/CT) imaging, cotinine (t1/2 20 h), carboxyhemoglobin (COHb) marker for tobacco cigarette, but not e-cigarette use; inflammatory markers, including C-reactive protein (CRP) and fibrinogen; the following antioxidant parameters: paraoxonase-1 activity, ((PON-1 activity) a protective ester hydrolase enzyme associated with HDL in blood that prevents the formation of oxidized LDL, LDL Oxidizability ((LDL-Ox) indicative of susceptibility of apoB-containing lipoproteins to oxidation and HDL antioxidant/anti-inflammatory capacity, expressed as a HDL antioxidant index ((HOI) which assesses the ability of HDL to inhibit LDL oxidation.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cardiovascular disease
		The authors reported that both hematopoietic tissue metabolic activity and aortic wall metabolic activity are increased in tobacco and e-cigarette users, and that plasma cotinine, an estimate of tobacco cigarette and e-cigarette burden, was weakly correlated with bone marrow activity. The authors concluded that the findings indicated activation of the Splenocardiac Axis in a graded manner, from non-user, healthy control subjects, to habitual e-cigarette users, to tobacco cigarette smokers.[221] Device and products: Not reported
Alzahrani *et al*.[222] 2018	Harm	The authors reported on the relationship between **e-cigarette use and myocardial infarction.** Age: 18 plus years. Sex: 38,209 females. Country: USA. Ethnicity: Hispanic 9826 White 46242 Black 8667 Asian 3769 Other 948 Data source: National Health Interview Survey Population size: 36,697 (2014) 33,028 (2016) Data collection period: 2014 and 2016 E-cigarette, smoking and other related status: E-cigarette use were grouped as never, former, some days and daily. Each of the four groups were further sub-grouped according to cigarette use status. Thus the 16 groups were: never electronic use never cigarette smoker, never electronic use former cigarette smoker, never electronic use someday cigarette smoker, never electronic use daily cigarette smoker; former electronic use never cigarette smoker, former electronic use former cigarette smoker, former electronic use someday cigarette smoker, former electronic use daily cigarette smoker; some days electronic use never cigarette smoker, some days electronic use former cigarette smoker, some days electronic use someday cigarette smoker, some days electronic use daily cigarette smoker; and daily electronic use never cigarette smoker, daily electronic use former cigarette smoker, daily electronic use someday cigarette smoker, daily electronic use daily cigarette smoker. 25.8% of current (some days or daily) e-cigarette users were former smokers and 66.2% of current e-cigarette users were current (some days or daily) cigarette smokers; current e-cigarette users were less likely to be daily users (34.4% or 776/2,259) than were current cigarette smokers (76.5% or 8,969/11,718, p<0.001). Outcomes: Myocardial infarction. Controlling for the demographic characteristics of age, gender, Body Mass Index (BMI) and several health characteristics (hypertension, diabetes, and hypercholesterolemia) e-cigarette use was independently associated with increased odds of having had a myocardial infarction (OR=1.79, 95% CI=1.20, 2.66, p=0.004) as was daily conventional cigarette smoking (OR=2.72, 95% CI=2.29, 3.24, p<0.001) The authors concluded that e-cigarette use was independently associated with increased odds of having had a myocardial infarction.[222] Device and products: Not reported
Wang et al.[224] 2018	Harm	The authors reported on the relationship between **cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms**. Age: median 41.4 years (E-cigarette use only), median 45 years cigarette use only, 46 years dual user Sex: 27,600 females, 12,047 males. Country: Mostly USA Ethnicity: Non-Hispanic White 32,302, Hispanic 2,761, Black/African-American 2,014, Asian 1,723, Other 445

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cardiovascular disease
		Data source: Health e-Heart Study. Population size: 39,747 Data collection period: March 8, 2013 to March 1, 2017 E-cigarette, smoking and other related status: 573 (1.4%) reported e-cigarette only use, 1,693 (4.3%) reported cigarette only use, and 514 (1.3%) dual use. Outcomes: Nineteen cardiopulmonary symptoms: breathing difficulty, chest pain, palpitations, loss of consciousness or syncope, high blood pressure or hypertension, high cholesterol, diabetes, coronary artery disease/ angina, heart attack, blocked arteries (legs), blood clots (veins or lungs), congestive heart failure, stroke or TIA (transient ischemic attack), enlarged heart, atrial fibrillation, arrhythmia, sleep apnoea, COPD, asthma, or cardiac arrest. The SF-12 general health score, measuring 19 cardiopulmonary symptoms, was lower (worse) in dual users compared to cigarette-only users; this was specifically observed in the outcomes of breathing difficulties and a history of arrhythmia. E-cigarette-only use, compared to no product use, was associated with lower general health scores, higher breathing difficulty scores (typically and in the past month), and greater proportions of those who responded 'yes' to having chest pain, palpitations, coronary heart disease, arrhythmia, chronic obstructive pulmonary disease, and asthma. The authors suggested that the use of e-cigarettes alone may have contributed to cardiopulmonary health risks, particularly respiratory health risks.[224] Device and products: Not reported
Farsalinos et al.[223] 2019	Unable to determine	The authors reported on the relationship between **e-cigarette use, coronary heart disease, and myocardial infarction.** Age (SD): Daily 43.3(15.7), Some days 41.2(15.5), Former 41.0 (15.6), Never 52.2(18.6) Sex: 58.2% males, 41.8% females. Country: USA. Ethnicity: White, Black or African American, American Indian or Alaska Native (AIAN), Asian, and Multiple Race Data source: National Health Interview Surveys Population size: 33,028 (2016) and 26,742. Data collection period: 2016 and 2017 E-cigarette, smoking and other related status: Daily (714), Some days (1,009), Former (7,026), Never (50,830) Outcomes: participants informed reporting of receiving a diagnosis of coronary heart disease and myocardial infraction from a doctor The authors concluded that the pooled analysis of the 2016 and 2017 National Health Interview Survey showed no association between e-cigarette use and myocardial infarction or coronary heart disease. The associations between established risk factors, including smoking, and both conditions were remarkably consistent. The inconsistent associations observed in single-year surveys and the cross-sectional design of the National Health Interview Survey cannot substantiate any link between e-cigarette use and an elevated risk for myocardial infarction or coronary heart disease.[223] Device and products: Never smokers were defined in the survey based on a cut-off point of using 100 cigarettes in their life (participants were asked 'Have you smoked at least 100 cigarettes in your entire life?'). Those responding 'no' were classified as never smokers. Those responding 'yes' were subsequently asked about current smoking (participants were asked 'Do you now smoke cigarettes every day, some days, or not at all?'). This

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cardiovascular disease
		question was used to define daily and some days smokers, while former smokers were defined as those responding 'yes' to the question about ever smoking and 'not anymore' to the question about current smoking. Ever e-cigarette use was determined by asking: 'Have you ever used an e-cigarette even one time?'. Those responding 'no' were classified as never users. Those responding 'yes' were subsequently asked about current e-cigarette use (participants were asked 'Do you now use e-cigarettes every day, some days, or not at all?'). This question was used to define daily and some days e-cigarette users, while former e-cigarette users were defined as those responding 'yes' to the question about ever e-cigarette use and 'not anymore' to the question about current e-cigarette use. No other device or product specific information was gathered[223]
Osei *et al.*[225] 2019a	Possible benefit	The authors reported on the association between **e-cigarette use and cardiovascular disease**. Age: Median age group of current users 30 to 34 median age group of current never users 45 to 49 years Sex: 41.2% female in the current users, 55.2% female in the never users Country: USA. Ethnicity: White 69.7%, Black 9.1%, Asian 3.7%, Hispanic 12.1%, Others 5.4 % in the current users, White 60.5%, Black 12.4%, Asian 6.5%, Hispanic 17.9%, Others 2.7 % in the never users Data source: Behavioural Risk Factor Surveillance System Population size: 449,092. Data collection period: 2016 and 2017 E-cigarette, smoking and other related status: 15,863 (3.5%) current e-cigarette users, 12,908 (2.9%) dual users of e-cigarettes + combustible cigarettes, Outcomes: Cardiovascular Disease and Premature Cardiovascular Disease Of the 449,092 participants, 44,852 (10.0%) had cardiovascular disease. The authors reported that dual use of e-cigarettes + combustible cigarettes was associated with significantly higher odds of cardiovascular disease compared with smoking alone. They also found a graded increase in odds of cardiovascular disease with increasing frequency of e-cigarette exposure among current combustible-cigarette smokers. No significant association between e-cigarette use and cardiovascular disease among never combustible cigarette smokers. However, current combustible cigarette smokers who never used e-cigarettes, dual use of e-cigarettes plus combustible cigarettes was associated with 36% higher odds of cardiovascular disease (Odds Ratio [OR], 1.36; 95% CI, 1.18-1.56); with consistent results in subgroup analyses of premature cardiovascular disease in women less than 65years and men less than 55years old. That is higher odds of cardiovascular disease among dual users of e-cigarettes + combustible cigarettes compared to smoking alone. The authors concluded that their results suggest significantly higher odds of cardiovascular disease among dual users of e-cigarettes and combustible cigarettes compared with combustible tobacco cigarette-only users. They also queried whether the current lack of significant association between e-cigarette use and cardiovascular disease among never combustible cigarette smokers may be due to the younger age of this group.[225] Device and products: Not reported

Table 69: Cross-sectional surveys papers on cancers, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cancers
Franco et al.[228] 2016	Harm, but less harm than tobacco cigarettes	The authors reported on the relationship between **e-cigarettes and micronuclei prevalence indicative of oral cavity cancer** following cytologic examination of oral mucosa. Age: average years (range) smokers 47.6 (23–73), 57.8 (27–65), 46.7 (23–74) Sex: males 10 smokers, 12 e-cigarette smokers and 11 non-smokers, females 13 smokers, 10 e-cigarette smokers and 9 non-smokers Country: Italy. Data source: Hospital outpatient attendees Population size: 65 Data collection period: January and June 2015 E-cigarette, smoking and other related status: smokers (n=23), e-cigarette smokers (n=22) and non-smokers (n=20). Smokers only subjects who consumed a single type of cigarette were included in the study, cigarettes were classified according to the average content of nicotine and tar, e-cigarette smokers used different e-cigarette devices and various types of charging liquid. The e-cigarette smokers considered did not use the conventional combustible tobacco cigarette in the last six months. Thus, e-cigarettes were classified according to the nicotine content of the charging liquid: light (0.4–0.9 mg), medium (0.10–0.12 mg), and heavy (0.13–0.16 mg). Outcomes: Micronuclei A higher prevalence of micronuclei was observed in smokers relative to e-cigarette smokers, and non-users had the lowest prevalence of micronuclei among the three groups. The authors stated that micronuclei are indicative elements of genomic instability and may have a clinical application in screening tests for risk categories of oral cavity carcinoma. They also suggested that e-cigarettes seem to be safe for oral cells and should be suggested as an aid for smoking cessation.[228] Device and products: Group B (e-cigarette users) included subjects who used different e-cigarette devices and various types of charging liquid. The e-cigarette smokers whom we have considered did not use the conventional combustible tobacco cigarette in the last six months. Thus, e-cigarettes were classified according to the nicotine content of the charging liquid: light (0.4–0.9 mg), medium (0.10–0.12 mg), and heavy (0.13–0.16 mg). For each consumer, the content (mL) of the reservoir of the device and the number of daily refills were evaluated. Group A (Conventional cigarette users), specific data on cigarette consumption were collected from each subject, including daily and yearly consumption, type of cigarette, possible side effects, and period of consumption or withdrawal. Cigarette consumption was calculated according to the number of cigarettes smoked in 24 hours and the number of packs consumed yearly by using the formula: packages/year = (number of cigarettes smoked per day: 20) × year of consumption. Only subjects who consumed a single type of cigarette were included in the study. Cigarettes were classified according to the average content of nicotine and tar
Shahab et al.[226] 2017	Harm, but less harm than tobacco cigarettes for one indicator	The authors reported on the relationship between smokers of **combustible cigarettes** only, former smokers with long-term **e-cigarette-only** use, former smokers with long-term NRT-only use, long-term dual users of both combustible cigarettes and e-cigarettes, and long-term users of both combustible cigarettes and NRT with **exposure to nicotine, tobacco-related carcinogens, and toxins**. Age: Mean age years 37.8. Sex: 100 males 71 females. Country: United Kingdom Ethnicity: White 131 Data source: Purposively recruited individuals

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cancers
		Population size: 171. Data collection period: January 2014 to June 2014 E-cigarette, smoking and other related status: combustible cigarette-only users, former smokers with long-term (≥6 months) e-cigarette-only or nicotine replacement therapy--only use, and long-term dual combustible cigarette-e-cigarette or combustible cigarette-nicotine replacement therapy users. Smokers: Cigarette-Only Users (n _ 37) Dual Cigarette–NRT Users (n _ 36) Dual Cigarette–e-cigarette Users (n _ 36) Former Smokers: NRT–Only Users (n _ 36) e-cigarette-Only Users (n _ 36) Outcomes: biomarkers of nicotine, tobacco specific N-nitrosamines (TSNAs), and volatile organic compounds specifically the parent Compound (biomarker/metabolite) Acrolein (N-acetyl-S-(3-hydroxypropyl)-L-cysteine), Acrylamide (N-acetyl-S-(2-carbamoylethyl)-L-cysteine), Acrylonitrile (N-acetyl-S-(2-cyanoethyl)-L-cysteine), 1,3-butadiene (N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine), Ethylene oxide (N-acetyl-S-(2-hydroxyethyl)-L-cysteine). Across the five groups (n=36–37 per group), nicotine, carcinogen, and toxin exposure was assessed using urine and saliva samples, which were analysed for biomarkers of nicotine, tobacco-specific N-nitrosamines (TSNAs), and volatile organic compounds. The authors concluded that e-cigarette-only users had significantly lower 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels than all other groups. Combustible cigarette-only users, dual combustible cigarette and NRT users, and dual combustible cigarette and e-cigarette users had largely similar levels of tobacco-specific N-nitrosamines and volatile organic compounds metabolites. Device and products: Product use was verified by asking participants to bring in the NRT or e-cigarette that they were currently using, and smoking status was verified with carbon monoxide readings (10-ppm cutoff).[226]
Bustamante et al.[229] 2018	Harm, but less than tobacco cigarettes	The authors reported on the relationship between **e-cigarette** use and the presence of N'-nitrosonornicotine (NNN) as a **risk marker of oral and oesophageal cancer.** Age: mean 31.3 years e-cigarette users 41.9 years non-smokers 40.6 years smokers Sex: 8 e-cigarette users 12 years non-smokers 14 years smokers Country: USA. Ethnicity: White 20 e-cigarette users 10 non-smokers 16 smokers, Other 10 smokers 3 non-smokers, Non-Hispanic 20 cig users 20 non-smokers 19 smokers Data source: E-cigarette users, smokers, and non-smokers were recruited by the University of Minnesota Tobacco Research Programs Population size: 59. Data collection period: Not reported E-cigarette, smoking and other related status: 20 e-cigarette users, 20 smokers, and 19 non-smokers. E-cigarette users were daily users who reported at least three months of exclusive e-cigarette use and no other tobacco use in the past 6 months. A smoker was classified as such if he/she smoked at least 10 cigarettes per day and had no regular use of nicotine replacement therapy products and no other tobacco or e-cigarette use in the last 6 months, participants were classified as non-smokers if they smoked less than 100 cigarettes in their lifetime and had no tobacco or e-cigarette use in the last 6 months. Outcomes: N'-nitrosonornicotine (NNN), nornicotine, and nicotine in saliva samples, N'-nitrosonornicotine (NNN), nornicotine, and nicotine in urinary samples

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cancers
		The mean of N'-nitrosonornicotine (NNN) in saliva of e-cigarette users was 14.6 (+/-23.1) pg/mL, ranging from nonquantifiable (below the limit of quantitation, LOQ) to 76.0 pg/mL. In smokers, salivary NNN ranged from below LOQ to 739 pg/mL, with 80% of smokers having salivary NNN in the range of levels found in e-cigarette users. Very low levels of urinary total N'-nitrosonornicotine (NNN) were present in only 5 out of 20 e-cigarette users (ranging from 0.001 to 0.01 pmol/mL urine). The authors concluded that N'-nitrosonornicotine is formed endogenously in e-cigarette users, and while overall exposure to N'-nitrosonornicotine in e-cigarette users is lower than in smokers, the known carcinogenic potency of N'-nitrosonornicotine should be monitored (specifically salivary rather than urinary NNN) in order to assess the potential relationship of e-cigarettes with oral and oesophageal cancers.[229] Device and products: Not reported
Carroll et al.[230] 2018	Harm	The authors reported on the relationship of **cigarette smokers and electronic nicotine delivery system (ENDS) users with nicotine metabolism and nicotine and carcinogen exposure.** Age: Median age 46 years cigarette smokers, 33 ENDS users, 40 Dual users Sex: Females 33/73 Cigarette smokers 16 ENDS users 17 Dual users Country: USA, adults of American Indian descent Data source: Community-based recruitment of adults of American Indian descent Population size: 73. Data collection period: USA. E-cigarette, smoking and other related status: smokers (n=27), electronic nicotine delivery system (ENDS) users (n=21), and dual users (n=25). A regular cigarette smoker was defined as an individual who smoked at least 5 cigarettes per day for the past 3 months and in the past 24 h and had not used tobacco products other than cigarettes in the past 3 months. A regular ENDS user was defined as an individual who used an ENDS daily for the past 3 months and in the past 24 h and had not used tobacco products other than ENDS in the past 3 months. A dual user was defined as an individual who smoked at least 5 cigarettes per day in the past 3 months and in the past 24 h, used an ENDS product daily for the past 3 months and in the past 24 h, and not used tobacco products other than cigarettes and ENDS in the past 3 months.[230] Outcomes: nicotine metabolism (nicotine metabolite ratio [NMR]), nicotine dose (total nicotine equivalents [TNE]), and a tobacco-specific lung carcinogen (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides [total NNAL] Among smokers, there were inverse relationships between nicotine metabolite ratio and total nicotine equivalents (r=-0.45) and between nicotine metabolism nicotine metabolite ratio and (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides [NNAL] (r=-0.50). Among dual users, nicotine metabolism, nicotine metabolite ratio and total nicotine equivalents, and nicotine metabolite ratio and (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides were not associated. Among ENDS users, nicotine metabolism, nicotine metabolite ratio and total nicotine equivalents were not associated. The authors concluded that the high prevalence of smoking and ENDS use among American Indians in the southern plains may not be related to nicotine metabolism. Environmental and social cues may play a more

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers cancers
		important role in light tobacco users, and this may be particularly true among American Indian light tobacco users who have strong cultural ties.[230] Device and products: Participants were asked to complete the following: You said you currently use an electronic nicotine product. These products are battery-powered, use nicotine fluid rather than tobacco leaves, and produce vapor instead of smoke. There are many different names for these devices. Some common brands include Fin, NJOY, Blu, e-Go and Vuse.' Then, generic photos of commonly used ENDS ('cig-a-like'; tank or vapor system; e-cigar; e-pipe; e-hookah) were displayed and participants were asked to choose the photo(s) which best resembled the ENDS they currently used. Participants had the option of selecting more than one ENDS. Information on Type of ENDS: tank/mod or vapor system, and, ENDS nicotine concentration was reported.
Chaffee et al.[227] 2019	Harm	The authors examined assessed tobacco product use (smokeless, combustible, and electronic cigarettes) and nicotine and carcinogen exposures**.** Age: Mean age years 15.8. Sex: All males. Country: USA Data source: study participants were male baseball players at 36 rural California high schools Population size: 594. Data collection period: 2014 to 2016 E-cigarette, smoking and other related status: Representative images and brief descriptions were shown for seven tobacco products: cigarettes, cigars, e-cigarettes (including cigarette-like disposable, rechargeable, and larger refillable devices), waterpipe (hookah), snus, dissolvable tobacco, and smokeless tobacco (moist snuff and chewing tobacco, listed in surveys as dip and chew, respectively). For each tobacco product, questions included: "Have you ever tried [tobacco product]? "During the past 30 days, on how many days did you use [tobacco product]?"; and "During the past 7 days, on how many days did you use [tobacco product]?" Individuals reporting past 30-day use of smokeless tobacco were asked to indicate the type (moist snuff, chewing tobacco, or both), the "brand of smokeless tobacco you use most often" (choose from a list or "other"), and the flavour (if any) of the smokeless tobacco usually used (choose from a list or "other"). Outcomes: Salivary specimens were assayed for cotinine (a biomarker of nicotine exposure) and urine specimens for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL, a biomarker of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) The authors concluded that adolescents who use **smokeless tobacco products (including e-cigarettes)** are exposed to substantial levels of nicotine and to the biomarker of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Although exposed to lower levels than adult smokeless tobacco product users, the findings are concerning given the young age of the sample and the tendency for smokeless tobacco product users to increase use intensity over time.[227] Device and products: Not reported

Table 70: Cross-sectional surveys papers on respiratory diseases, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		Respiratory symptoms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
Wang et al.[233] 2016	Harm	The authors reported on the relationship between **e-cigarette use and respiratory symptoms**. Age: mean (SD) age was 14.6 (1.9) years. Sex: 51.1% males Country: Hong Kong. Ethnicity: Chinese Data source: Secondary students. Population size: 44,662. Data collection period: 2012 -2013 E-cigarette, smoking and other related status: Smoking status was defined as never-smoking (36 915), ever-smokers (7048) experimental smoking (smoked once or a few times) (3576), ex-smoking (smoked in the past but not now) (1812), and current smoking (smoked on ≥1 day in the past 30 days) (1660). Use of e-cigarettes in the past 30 days (yes or no), respiratory symptoms (cough or phlegm) for 3 consecutive months in the past 12 months (yes or no), sociodemographic characteristics (sex, age, and perceived family affluence), and second-hand smoke exposure were recorded. Outcomes: respiratory symptoms (cough or phlegm) for 3 consecutive months in the past 12months (yes or no) Adjusted odds ratios (AORs) of respiratory symptoms - cough or phlegm. E-cigarette use was significantly associated with respiratory symptoms (AOR, 1.28; 95% CI, 1.06-1.56). The corresponding AORs (95% CIs) were 2.06 (1.24-3.42) in never-smokers, 1.39 (1.14-1.70) in ever-smokers, and 1.40 (1.02-1.91) in ex-smokers. Positive but nonsignificant associations were observed in experimenters (AOR, 1.09; 95% CI, 0.66-1.80) and current smokers (AOR, 1.15; 95% CI, 0.81-1.62). The authors noted that the strong association of respiratory symptoms (cough or phlegm for 3 consecutive months in the past 12 months) in adolescent e-cigarette users who never smoked tobacco cigarettes (AOR: 2.06; 95% CI: 1.24–3.42) is comparable with that found in adolescent occasional smokers (AOR: 1.72; 95% CI: 1.01–2.93) in other Hong Kong study populations.[233] Device and products: Not reported
McConnell *et al*.[238] 2017	Harm	The authors reported on the relationship of **e-cigarette use with chronic bronchitis symptoms and wheeze** in an adolescent population. Age: Mean age 17.3 years (SD, 0.6). Sex: Not reported. Country: USA Data source: Southern California Children's Health Study Population size: n = 2,097; 87% of 2,412 members of the cohort attending schools in the study communities. 2,086 provided information on e-cigarette use and either wheeze or bronchitic symptoms. Data collection period: 2014. E-cigarette, smoking and other related status: Ever e-cigarette use was reported by 502 (24.0%), of whom 201 (9.6%) used e-cigarettes during the last 30 days (current users) Outcomes: Risk of bronchitic symptoms was increased by almost twofold among past users of e-cigarettes (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.37–2.49), compared with never-users of e-cigarettes, and by 2.02-fold (95% CI, 1.42–2.88) among current users of e-cigarettes. Risk increased with frequency of current use (OR, 1.66; 95% CI, 1.02–2.68) for 1–2 days and 2.52 (95% CI, 1.56–4.08) for 3 or more days in past 30 days compared with never-users. Associations were attenuated by adjustment for lifetime number of cigarettes smoked and second-hand smoke exposure.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		However, risk of bronchitic symptoms among past of e-cigarettes users remained elevated after adjustment for relevant potential confounders and was also observed among never–cigarette users (OR, 1.70; 95% CI, 1.11–2.59). There were no statistically significant associations of e-cigarette use with wheeze after adjustment for cigarette use. Examination of interactions of e-cigarette use with sex, ethnicity (Hispanic and non-Hispanic white), and asthma and with a dog or cat in the home, was also undertake none of which was statistically significant. The authors concluded that adolescent e-cigarette users had increased rates of chronic bronchitic symptoms.[238] Device and products: Not reported
Hedman et al.[234] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the association of **e-cigarette use** with smoking habits, demographic factors, and **respiratory symptoms** (such as sputum production, chronic productive cough, and wheeze). Age: 20 to 75 years, Sex: 13,947 males, 16,325 females. Country: Sweden Data source: Obstructive Lung Disease in Northern Sweden study Population size: 30 272. Data collection period: 2016 E-cigarette, smoking and other related status: The number of current smokers was 3694 (12.3%), and 7305 (24.4%) were former smokers. Outcomes: Respiratory symptoms were defined by affirmative answers to the following questions: for long-standing cough, “Have you had long-standing cough during the last year?”; for sputum production, “Do you usually have phlegm when coughing, or do you have phlegm in your chest that is difficult to bring up?”; for chronic productive cough, “Do you bring up phlegm on most days during periods of at least 3 months?” and “Have you had such periods during at least 2 successive years?”; for any wheeze, “Have you at any time during the last 12 months had wheezing or whistling in your chest?”; for recurrent wheeze, “Do you usually have wheezing, whistling, or a noisy sound in your chest when breathing?”; and for any respiratory symptoms, an affirmative answer to any of Respiratory symptoms (long-standing cough, sputum production, chronic productive cough, any wheeze, recurrent wheeze, any respiratory symptoms) were most common among dual users of conventional combustible tobacco cigarettes and e-cigarettes, and among former smokers and non-smokers who used e-cigarettes. In a regression analysis adjusted for sex, age group, survey, and educational level, having any respiratory symptoms was significantly associated with dual use (OR: 4.03; 95% CI: 3.23–5.02), smoking only (OR: 2.55; 95% CI: 2.36–2.77), and former smoking without e-cigarette use (OR: 1.27; 95% CI: 1.19–1.36), while former smoking with e-cigarette use (OR: 1.47; 95% CI: 0.91–2.37) and non-smoking with e-cigarette use (OR: 1.46; 95% CI: 0.93–2.29) did not reach statistical significance. Non-smokers without e-cigarette use were used as the reference in the regression analysis.[234] Device and products: Not reported
Lestari *et al.*[235] 2018	Harm	The authors reported on the relationship between **e-cigarette use**, a range of **subjective feelings of upper respiratory well-being,** and **formaldehyde vapour concentration**. Age: 18 to 25 years. Sex: Not reported. Country: Indonesia. Data source: Purpose sampling. Population size: 20 Data collection period: October 2015 to December 2016.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		E-cigarette, smoking and other related status: The sample consisted of active e-cigarettes smokers who have been smoking for at least 2 months as members of electronic cigarette community. Outcomes: Subjective feelings during smoking e-cigarettes such as irritation in nose, eye, and throat. Nose irritation - itchy nose, uncomfortable smell, and sneezing. Eye irritation - watery eye, sore eye, and reddish eye. Upper airway irritation - sore throat, dry throat, cough, and asphyxia. Health complaints were obtained by interviews using questionnaires. The specific health complaints irritation and number reporting the condition were: irritation in nose (Itchy nose n=3, sneezing n=4, uncomforted smell n=1), eye, (reddish n=0, sore=1 watery n=1) and throat (upper airway irritation – asphyxia n=1, cough n=5, dried throat n=13, sore throat n=2). Cotinine urine was positive in 88.0% of participants. A variety of vapours were assessed: vapor 1 (local vapor) contained 90% glycerine and 10% propylene glycol, vapor 2 (USA) contained 60% glycerine and 40% propylene glycol, vapor 3 (Malay) contained 60% glycerine and 40% propylene glycol, vapor 4 (local vapor) contained 60% glycerine and 40% propylene glycol, vapor 5 (Malay) contained 30% glycerine and 70% propylene glycol, vapor 6 contained 70% glycerine and 30% propylene glycol in e-cigarettes. The duration of formaldehyde measurement was 60 minutes within the same smoking period in each measurement. Formaldehyde concentration varied from 0.0345 ppm to 0.1490 ppm. The health complaints were mostly upper airway irritation with acute effect and mostly cotinine urine was positive. The authors concluded that health complaints were mostly upper airway irritation with acute effect, and that cotinine in urine was mostly positive.[235] Device and products: The measurement of e-cigarettes brand was done to identify the formaldehyde concentration vapor in six brands of e-cigarettes that are liquid local 90(VG)/10 propylene glycol, liquid USA 60 propylene glycol)/40(VG), liquid Malay 60 propylene glycol/40(VG), liquid local 60 propylene glycol/40(VG), liquid Malay 30 propylene glycol/70(VG), and liquid USA 70 propylene glycol)/30(VG). Before measuring six vapours, in the beginning formaldehyde concentration was measured in empty glass container as a control. Formaldehyde vapor concentration was analysed at Occupational Safety and Health Laboratory
Reidel et al.[231] 2018	Harm	The authors reported on the relationship between cigarette smokers, **e-cigarette** users, and non-smokers **with the profile of innate defence proteins** in airway secretions of mucins MUC5AC and MUC5B, and of neutrophil extracellular trap formation rates. Age: Not reported. Sex: Not reported. Country: USA. Data source: Not reported Population size: 44. Data collection period: Not reported E-cigarette, smoking and other related status: 14 current cigarette smokers, 15 current e-cigarette users, and 15 never-smokers. The average number of cigarettes smoked per day in the cigarette smoker group was approximately 11. E-cigarette users had been using e-cigarettes actively and exclusively or predominantly for at least 6 months. In the e-cigarette user category, the average number of puffs inhaled per day was approximately 280. Of the 15 e-cigarette users, 12 identified themselves as having previously smoked cigarettes, and three indicated no prior cigarette smoking history. In addition, five of the subjects reported occasionally smoking cigarettes Outcomes: mucins MUC5AC and MUC5B, and neutrophil extracellular trap (NET) formation rates

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		Using induced sputum samples from cigarette smokers, e-cigarette users, and non-smokers total and individual concentrations of mucins MUC5AC and MUC5B and neutrophil extracellular trap (NET) formation rates were determined. E-cigarette users exhibited significant increases in aldehyde-detoxification and oxidative stress-related proteins associated with cigarette smoke compared with non-smokers. The levels of innate defence proteins associated with chronic obstructive pulmonary disease, such as elastase and matrix metalloproteinase-9, were significantly elevated in e-cigarette users as well. E-cigarette users' sputum also uniquely exhibited significant increases in neutrophil granulocyte-related and NET-related proteins, such as myeloperoxidase, azurocidin, and protein-arginine deiminase 4, despite no significant elevation in neutrophil cell counts. Peripheral neutrophils from e-cigarette users showed increased susceptibility to phorbol 12-myristate 13-acetate-induced NETosis. Finally, a compositional change in the gel-forming building blocks of airway mucus (i.e., an elevated concentration of mucin MUC5AC) was observed in both cigarette smokers and e-cigarette users. The authors concluded that e-cigarette use alters the profile of innate defence proteins in airway secretions, inducing similar and unique changes relative to cigarette smoking. These data challenge the concept that e-cigarettes are a healthier alternative to cigarettes.[231] Device and products: Not reported
Tuhanioglu *et al.*[250] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the effects of **e-cigarettes on voice performance** compared with conventional combustible tobacco cigarettes. Age: 18 to 54 years. Sex: Males. Country: Turkey Data source: Adana City Hospital otolaryngology clinic volunteers Population size: 81. Data collection period: Not reported E-cigarette, smoking and other related status: Three groups: e-cigarette users passed smoker of conventional tobacco cigarettes and electronic cigarette user for 1 to 3 years (group 1, n = 21), conventional cigarette users (group 2, n = 30), and non-smokers who had never smoked (group 3, n = 30). Outcomes: Fundamental frequency, jitter %, shimmer %, shimmer dB, harmonics-to-noise ratio (HNR) values, and Voice Handicap Index 10 The nicotine content of the e-cigarettes was 9 and 12 mg/mL and these smokers inhale 1–2 mL/d. Group 2 consisted of men who smoked 10–20 conventional tobacco cigarettes per day and had done so for 1–5 years. Volunteers in groups 1 and 2 were selected who were using 10–20 mg of nicotine per day. No significant difference regarding the Fundamental frequency, jitter %, and shimmer % values between the groups was detected. A significant difference was detected regarding the shimmer dB and harmonics-to-noise ratio values between the groups. The mean Voice Handicap Index 10 values of the conventional cigarette users were higher than those of the e-cigarette users and the control group ($P < 0.05$). The authors concluded that the effects of e-cigarettes on voice were detected as mild compared with those of conventional combustible tobacco cigarettes, according to the subjective and objective voice analysis results in the study.[250] Device and products: The nicotine content of the e-cigarettes was 9 and 12 mg/mL and these smokers inhale 1–2 mL/d.
King *et al.*[236] 2019	Harm	The authors reported on the **adverse symptoms identified in e-cigarette** users.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		Age: mean age years (SD) 37.9. Sex: 802 males, 820 females Country: USA. Ethnicity:1,140 white, 477 non-white Data source: nationally representative cross-sectional telephone survey of 4,964 US adults Population size: 1,624. Data collection period: August 2016 to May 2017 E-cigarette, smoking and other related status: ever e-cigarette users Outcomes: Cough, Dry Mouth or Throat, Dizziness or light-headedness, Headache or Migraine, Shortness of breath, Change in or loss of taste The authors concluded that most e-cigarette users reported at least one symptom, most commonly a cough or a dry or irritated mouth or throat. Former cigarette smokers who used e-cigarettes in the past 30 days were less likely than current or never-smokers to report adverse symptoms of e-cigarette use. Device and products: All participants were read this statement: "The next few questions are about electronic or e-cigarettes and other vaping devices, such as vape pens. Popular brands include Blu, Vuse, NJOY, and Flavour Vapes." Then, we asked participants whether they ever used an e-cigarette or other vaping devices, even one or two times. The authors asked participants who reported ever using e-cigarettes on how many of the past 30 days they used e-cigarettes. No further information on device or product was reported.[236]
Li *et al.*[237] 2019	Harm	The authors reported on the association between smokers, dual users, and **vapers with wheezing and related respiratory symptoms**. Age: Not reported. Sex: Not reported. Country: USA Data source: U. S. Population Assessment of Tobacco and Health Population size: 28,171 adults Data collection period: October 2014 to October 2015 E-cigarette, smoking and other related status: 641 (1.2%) were current vapers who used e-cigarettes exclusively, 8525 (16.6%) were current exclusive smokers, 1106 (2.0%) were dual users and 17 899 (80.2%) were non-users Outcomes: wheezing and related respiratory symptoms; specifically, ever had wheezing or whistling in chest at any time in past, wheezing or whistling in chest in past 12 months, number of wheezing attacks more than 12 in past 12 months, one or more nights per week had sleep disturbed due to wheezing, speech limited to only one or two words between breaths due to wheezing in past 12 months, chest has sounded wheezy during or after exercise and dry cough at night not associated with a cold or chest infection. Compared with non-users, risks of wheezing and related respiratory symptoms were significantly increased in current vapers (adjusted OR (aOR)=1.67, 95% CI: 1.23 to 2.15). Current vapers had significantly lower risk in wheezing and related respiratory symptoms compared with current smokers (aOR=0.68, 95% CI: 0.53 to 0.87). No significant differences were found between dual users and current smokers in risk of wheezing and related respiratory symptoms (aOR=1.06, 95% CI: 0.91 to 1.24). The authors concluded that vaping was associated with increased risk of wheezing and related respiratory symptoms. Current vapers had lower risk in wheezing and related respiratory symptoms than current smokers or dual users but higher than non-users. Both dual use and smoking significantly increased the risk of wheezing and related respiratory symptoms.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		The authors concluded that vaping was associated with increased risk of wheezing and related respiratory symptoms. Current vapers had a lower risk of wheezing and related respiratory symptoms than current smokers or dual users, but a higher risk than non-users. Both dual use and smoking significantly increased the risk of wheezing and related respiratory symptoms. Age: 18 to 65 year plus. Most current vapers were aged 18–34 years (52.06%). Most current smokers were aged 35–64 (56.63%).[237] Device and products: Not reported
Meo et al.[232] 2019	Harm, but less harmful than tobacco cigarettes	The authors reported on the impact of **e-cigarettes on lung function** and **fractional exhaled nitric oxide** (FeNO) among 60 young healthy male adults. Age: The mean age of the exposed group (ENDS users) and control group (non-e-smokers) was 27.07 ± 6.00 (mean ± SD) and 25.90 ± 7.72 years, respectively. Sex: All young healthy male adults. Country: Saudi Arabia Data source: participants from the various suburbs in the city of Riyadh Population size: 60. Data collection period: September 2016–September 2017 E-cigarette, smoking and other related status: 30 e-cigarette users, who were using nicotine containing e-liquid daily for at least the past 6 months and 30 male matched controls who had never tried e-cigarettes, regular cigarettes, or shisha Outcomes: Spirometry to assess lung function test parameters including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), forced expiratory ratio (FEV1/FVC), peak expiratory flow (PEF), forced expiratory flow—25% (FEF25%), forced expiratory flow—50% (FEF50%), forced expiratory flow—75% (FEF75%), forced expiratory flow 25%–75% (FEF25%–75%), and forced expiratory flow 75%–85% (FEF75%–85%). The study population was divided into two groups: group 1 (e-cigarette-exposed group) 30 daily e-cigarette users (age 27.07 +/- 6.00 [mean +/- SD] years), group 2 (control group) 30 who were not e-cigarette users (age 25.90 +/- 7.72 [mean +/- SD] years). The study population were neither current nor former traditional tobacco users. The lung function test parameters that were found to be significantly decreased in e-cigarette users compared to their control group were forced expiratory volume in the first second (FEV1), forced expiratory ratio (FEV1/FVC), forced expiratory flow-25% (FEF25%), forced expiratory flow-50% (FEF50%), forced expiratory flow-75% (FEF75%), forced expiratory flow-25%-75% (FEF25%-75%), and forced expiratory flow-75%-85% (FEF75%-85%). Fractional nitric oxide concentration in exhaled breath (FeNO) was also decreased in e-cigarette users, but it did not reach the level of significance. The authors concluded that e-cigarettes significantly impaired various lung function parameters and the pattern of impairment exhibited a peripheral obstructive airway involvement [232] The authors concluded that fractional exhaled nitric oxide was decreased in e-cigarette users, but it did not reach the level of significance. Also, the use of e-cigarettes significantly impaired various lung function parameters, and the pattern of impairment exhibited a peripheral obstructive airway involvement.[232] Device and products: Not reported
		Asthma

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
Cho et al.[241] 2016	Harm	The authors reported on findings regarding the association between **e-cigarette use and asthma** (students' self-reported doctor diagnosis in past 12 months). Age: mean age years (SD) 16.4 ±0.9. Sex: 17,997 females, 17,902 males. Country: South Korea Data source: The Tenth Korean Youth Risk Behaviour Web-based Survey from 800 middle and high schools in 2014 Population size: 35,904. Data collection period: 2014 E-cigarette, smoking and other related status: 'current e-cigarette users' (n = 2,513), 'former e-cigarette users' (n = 2,078), and 'never e-cigarette users' (n = 31,313). e-cigarette use was assessed by the question 'Have you ever used an e-cigarette in your life?' (yes/no). Answering no was classified as 'never user'. Respondents who answered in the affirmative were asked a follow-up question 'Have you used e-cigarettes in the past 30 days?'(yes/no). Answering yes was classified as 'current user' and answering no was classified as 'former user'. Similarly, cigarette smoking was assessed by the question 'Have you ever smoked, even one puff in your life?' (yes/no). Answering no was classified as 'never smoker'. Respondents who answered in the affirmative were asked a follow-up question 'In the past 30 days, how many days did you smoke?' Answering 'one or more days' was classified as 'current smoker', and answering 'none' was classified as 'former smoker.' Outcomes: asthma (self-reported doctor diagnosis) The authors compared 'current e-cigarette' users with 'never e-cigarette' users, the unadjusted OR for asthma was 2.36 (95% CI: 1.89-2.94). In order to control for the effect of conventional cigarette (CC) smoking, after stratifying the subjects by the three CC smoking categories (never CC, former CC, and current CC), within the 'never CC' category, the unadjusted OR for asthma for 'current e-cigarette' users was 3.41 (95% CI: 1.79-6.49), and the adjusted OR was 2.74 (95% CI: 1.30-5.78). The authors concluded that e-cigarette users have an increased association with asthma and are more likely to have had days absent from school due to severe asthma symptoms [241] Device and products: Not reported
Choi et al.[240] 2016	Harm	The authors reported findings on the association between **e-cigarette use and asthma**. Age: 16 years. Sex: Not reported for the subsection of the population examined in this paper. Country: USA Ethnicity: Non-Hispanic White Hispanic Native American Non-Hispanic Asian Non-Hispanic Black Other Data source: Florida Youth Tobacco Survey Population size: 36,085. Data collection period: 2012 E-cigarette, smoking and other related status: E-cigarette use was assessed by asking the participants if they had ever tried using an electronic cigarette (yes/no), and if they had used an electronic cigarette during the past 30 days (yes/no). E-cigarettes were described to the participants as "battery-operated devices that look, feel, and taste like a tobacco cigarette." Participants reported the number of days they had smoked cigarettes during the 30 days prior to the survey. Outcomes: asthma

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		Among students with asthma, e-cigarette use was more common among those in non-metropolitan and rural counties than those in metropolitan counties (p<0.05). Ever and past 30-day e-cigarette use was associated with cigarette smoking susceptibility among participants with asthma and those who never tried cigarettes (n=2,410; ever use, AOR=3.96, 95% CI=1.49, 10.56; past 30-day use, AOR=422.10, 95% CI=50.29, >999.99). Past 30-day e-cigarette use was associated with having an asthma attack in the past 12 months among participants with asthma (n=5,865, p<0.01). The authors concluded that e-cigarette use is more common among Florida high school youth with asthma and is associated with susceptibility to cigarette smoking.[240] Device and products: Not reported
Kim et al.[242] 2017	Harm	The authors reported on the association of **active and passive e-cigarette vaping with asthma**. Age: 12 to 18 years (deduced from other studies using same dataset) adolescents. Sex: 106497 females. Country: South Korea Data source: Korea Youth Risk Behaviour Web-based Survey Population size: 216,956 Data collection period: 2011, 2012 and 2013 E-cigarette, smoking and other related status: Active smoking was classified into 4 groups (0 days, 1-5 days, 6-19 days, and >=20 days a month). Passive smoking was also categorized into 4 groups (0 days, 1-2 days, 3-4 days, and >=5 days a week). E-cigarette was defined as yes or no in the last 30 days Outcomes: asthma Active vaping was significantly associated with asthma (AOR [95% CI] of smoking >=20 days/month = 1.57 [1.38-1.77], P < 0.001). Passive vaping was also related with asthma (AOR [95% CI] of smoking >=5 days/week = 1.40 [1.28-1.53], P < 0.001). E-cigarette showed positive relation with asthma, although the effects of past smoking history could not be excluded (AOR [95% CI] = 1.12 [1.01-1.26], P = 0.027). Age, sex, obesity, region of residence, exhaled carbon monoxidenomic level, and parental educational level were adjusted for as confounders. The authors concluded that the study demonstrated a positive association between e-cigarette use and an asthmatic episode in the past 12 months, and that this association was observed when adjustments for active and passive vaping exposure were included in the analysis. However, e-cigarette vaping in the past month was not significantly associated with lifetime asthma after adjusting for active and passive vaping. Active and passive vaping were thus considered to be more influential on previous asthma history than recent e-cigarette vaping. As a high proportion of e-cigarette smokers are generally previous active smokers, the effects of previous active vaping were high in this group.[242] Device and products: Not reported
Schweitzer et al.[239] 2017	Harm	Authors reported on the association of **e-cigarette with asthma**, controlling for cigarette smoking, marijuana use, and six demographic covariates. Age: mean age was 15.8 (SD = 1.2) years. Sex: 50% female Country: Hawaii USA. Ethnicity: 2% of the participants were American Indian or Alaska Native; 3% were Black or African American, 29% were Filipino, 39%

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		were Native Hawaiian or Other Pacific Islander, 16% were Japanese or Other Asian, and 11% were Caucasian. Data source: Hawaii Youth Risk Behaviour Survey (HYRBS) Population size: 6,089. Data collection period: 2015 E-cigarette, smoking and other related status: Cigarette smoking was assessed by "Have you ever tried cigarette smoking, even a few puffs?" (No/Yes) and "During the past 30 days, on how many days did you smoke cigarettes?" (7 response options: 0 days to all 30 days). E-cigarette use had the lead-in instruction, "The next two questions ask about electronic vapor products, such as blu, NJOY, or Starbuzz. Electronic vapor products include e-cigarettes, e-cigars, vape pipes, e-hookahs, and hookah pens." The items were "Have you ever used an electronic vapor product?" (No/Yes) and "During the past 30 days, on how many days did you use an electronic vapor product?" (7 response options, same as for cigarettes). Marijuana use was assessed with "How old were you when you tried marijuana for the first time?" (7 responses: Never tried to 17 years or older) and "During the past 30 days, how many times did you use marijuana?" (6 response options: 0 times to 40 or more times). The item on age of first marijuana use was recoded to never tried vs. tried at any age, providing an index for ever use of marijuana. Outcomes: asthma Current e-cigarette use was associated with currently having (vs. never having) asthma (adjusted odds ratio [aOR]=1.48, CI 1.26-1.74) and with previously having (vs. never having) asthma (aOR=1.22, CI 1.07-1.40). The authors concluded that e-cigarette use by adolescents is independently associated with asthma.[239] Device and products: Nothing in addition reporting above
AboElNaga [243] 2018	Harm	The author reported on the relationship between **e-cigarettes and specific respiratory outcomes**, including asthma control test, lung function, blood eosinophils, and airway immunoinflammatory phenotype. Age: Mean 30.07±4.97 years. Sex: 63 males and 67 females. Country: Egypt Data source: Outpatient Clinic of Chest Department of the October 6 University Hospital Population size: 130. Data collection period: Not reported E-cigarette, smoking and other related status: non-smokers (48 patients), current conventional combustible tobacco cigarette smokers (41 patients), and e-cigarette smokers (41 patients). Outcomes: Spirometry parameters [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, maximal mid expiratory flow, and peak expiratory flow rate (PEFR)] and asthma control test (ACT) score airways immunoinflammatory (Eosinophilic, Neutrophilic, Paucigranulocytic) phenotype and blood eosinophilic count. The asthmatic patients were reported to have significant differences in spirometry and distribution of sputum cell subtypes between non-smokers, current conventional combustible tobacco cigarette smokers, and e-cigarette users. The author stated that asthmatic smoker patients who smoke e-cigarettes develop mixed sputum subtype; there was no difference in the pulmonary function or asthma control of patients who smoke e-cigarettes compared with that observed in conventional smokers. The author concluded that asthmatic patients who continue to smoke conventional combustible tobacco cigarettes or replace them with e-cigarettes have a significant decline

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		in their pulmonary function, as recorded by spirometry parameters (FVC, FEV1, FEV1/FVC, maximal mid expiratory flow, and peak expiratory flow rate), and asthma control test score, in comparison with non-smoking asthmatic patients.[243] Device and products: Not reported
Osei *et al.*[244] 2019b	Harm	The authors reported on the relationship between **e-cigarette use and asthma** among never combustible cigarette smokers. Age: median age group of current e-cigarette users 18–24 years Sex: 224,774 males, 178,042 females. Country: USA Data source: Behavioral Risk Factor Surveillance System Population size: 402,822 Data collection period: 2016 and 2017 E-cigarette, smoking and other related status: 402,822 never combustible cigarette smokers, 3,103 (0.8%) current e-cigarette users Outcomes: odds of asthma among never combustible smoking e-cigarette users The authors concluded that there was an increased rate of asthma among never combustible cigarette smoker e-cigarette users, with 39% higher odds of self-reported asthma compared to never e-cigarette users (OR: 1.39; 95% CI: 1.15–1.68).[244] Device and products: Not reported
Perez et al.[245] 2019	Harm	The authors reported on the association of **e-cigarette use and asthma** in never- smokers. Age: Not reported. Sex: Not reported. Country: USA Data source: Behavioral Risk Factor Surveillance System Population size: 486,303 (2016) and 450,016 Data collection period: 2016 and 2017 E-cigarette, smoking and other related status: Defining e-cigarette users and never-smokers. Respondents were first asked, “Have you ever used an e-cigarette or other electronic ‘vaping’ product, even just one time, in your entire life?” Those who responded “no” were considered never e-cigarette users. Those who answered “yes” were categorized as ever e-cigarette users, and then asked: “Do you now use e-cigarettes or other electronic ‘vaping’ products every day, some days, or not at all?” Ever e-cigarette users who responded “every day” were characterized as current e-cigarette daily users and those who reported “some days” were categorized as current e-cigarette someday users, while those who answered "not at all" were categorized as former e-cigarette users. Participants were considered never smokers of conventional tobacco cigarettes if they answered "no" to "Have you smoked at least 100 cigarettes in your entire life?” Outcomes: medical diagnosis of asthma as reported by participant The authors concluded that their findings suggest that e-cigarette use may be associated with asthma among never-smokers.[245] Device and products: Not reported
		Other chronic respiratory conditions

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
Martin et al.[248] 2016	Harm	The authors reported on the relationship between non-smokers, cigarette smokers, and **e-cigarette users** and **immune gene expression profiles** assessed from nasal scrape biopsies, nasal lavage, urine, and serum. Age: 18 to 50 years of age. Sex: 18 males, 21 females. Country: USA Data source: USA. Population size: 39. Data collection period: Not reported E-cigarette, smoking and other related status: non-smokers not regularly exposed to second-hand smoke (control group) (13), self-described active cigarette smokers (smoker group) (14) and self-described, active e-cigarette users/vapers (12) who had been using e-cigarettes regularly for at least 6 mo. Dual users smoking more than 5 cigarettes/week in addition to using e-cigarettes were excluded from these studies Outcomes: Serum cotinine and urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels. Epithelial RNA was isolated and analysed for differential cell to quantify neutrophils. All genes with decreased expression in cigarette smokers (n = 53) were also decreased in e-cigarette smokers. Additionally, vaping e-cigarettes was associated with suppression of many unique genes (n = 305). Furthermore, the e-cigarette users showed a greater suppression of genes common with those changed in cigarette smokers especially suppressed expression of transcription factors, such as EGR1, which was functionally associated with decreased expression of 5 target genes in cigarette smokers and 18 target genes in e-cigarette users. The authors concluded that the data indicate that vaping e-cigarettes is associated with decreased expression of a large number of immune-related genes, which are consistent with immune suppression at the level of the nasal mucosal.[248] Device and products: Not reported
Wills et al.[246] 2019	Harm	The authors reported on the association of **e-cigarette use with diagnosed respiratory disorders**. Age: mean age of 55 year Sex: 4,314 female, 3,772 male, 1 missing Country: Hawaii, USA. Ethnicity: Hawaiian 1,096, Filipino 1,026, Japanese 1,518, Chinese 379, Pac. Islander 185, Other Asian 160, Caucasian 3,374, Black 104, missing 245. Data source: Behavioural Risk Factor Surveillance Survey (BRFSS) Population size: 8,087. Data collection period: 2016 E-cigarette, smoking and other related status: A clarifying instruction prior to asking the e-cigarette items stated: “Electronic-cigarettes and other ‘vaping’ products include electronic hookahs (e-hookahs), vape pens, e-cigars, and others. These products are battery powered and usually contain nicotine and flavours such as fruit, mint, or candy.” The item on ever e-cigarette use asked, “Have you ever used an electronic cigarette or other electronic ‘vaping’ product in your entire life.” (Yes/No/Not Sure). The item on current use asked, “Do you now use e-cigarettes or other electronic ‘vaping’ products every day, some days, or not at all.” A clarifying instruction prior to the cigarette items stated: “For cigarettes do not include e-cigarettes (e-cigarettes, NJOY, Bluetip), herbal cigarettes, cigars, cigarillos, little cigars, pipes, bidis, kreteks, water pipes (hookahs), or marijuana.” The basic item on cigarette smoking asked, “Have you smoked at least 100 cigarettes in your entire life?” (Yes/No/Not Sure). Persons who answered Yes to this question

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		were then asked about current smoking: "Do you now smoke cigarettes every day, some days, or not at all." Persons who indicated current smoking (some days or every day) were asked, "During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking" (Yes/No). Persons answering Yes to lifetime smoking but No to current smoking were asked, "How long has it been since you last smoked a cigarette?" (7 options, within past month to 10 years or more). Outcomes: diagnosed respiratory disorder (asthma, chronic obstructive pulmonary disease). The adjusted Odd Ratio of e-cigarette use with chronic pulmonary disorder was adjusted Odd Ratio = 2.58, CI 1.36-4.89, $p < 0.01$ in the total sample and adjusted Odd Ratio = 1.33, CI 1.00-1.77, $p < 0.05$ in non-smokers. The associations were stronger among non-smokers than among smokers. The authors concluded that the study showed a significant independent association between e-cigarette use and chronic respiratory disorders. The association was stronger among non-smokers than among smokers. Device and products: Not reported
		Lung injury
Ghinai et al.[247] 2019	Harm	In July 2019, the Illinois Department of Public Health and the Wisconsin Department of Health Services launched a coordinated epidemiologic investigation after receiving **reports of several cases of lung injury** in previously healthy persons who reported using e-cigarettes or vaping. The Centers for Disease Control and Prevention reported the precise source of the outbreak as currently unknown; however, the predominant use of prefilled tetrahydrocannabinol-containing cartridges among patients with lung injury associated with e-cigarette use suggested that these products played an important role. Centrers for Disease Control and Prevention recommended that persons consider refraining from using e-cigarette, or vaping, products, particularly those containing tetrahydrocannabinol. Given the diversity of products reported and frequency of patients using both tetrahydrocannabinol - and nicotine-containing e-cigarette products, additional methods such as product testing and traceback could help identify the specific cause of this outbreak[247] Device and products: Numerous products and brand names were identified by patients
		Passive smoking
Bayly et al.[249] 2019	Harm	The authors reported on the relationship between second-hand **e-cigarette aerosol exposure and asthma exacerbations** among youth with asthma. Age: 11-17 years. Two-thirds were aged 11 to 13 years. Sex: 50% female Country: USA. Data source: Florida Youth Tobacco survey Population size: N = 11,830. Data collection period: 2016 E-cigarette, smoking and other related status: second-hand exposer to ENDS Outcomes: salivary cotinine Youth who participated in the 2016 Florida Youth Tobacco survey (aged 11-17 years) with a self-reported diagnosis of asthma (N = 11,830) reported asthma attacks in the past 12 months, demographic characteristics, cigarette use, cigar use, hookah use, ENDS use, past 30-day second-hand smoke exposure, and past 30-day second-hand ENDS aerosol exposure were assessed for exposure to nicotine. The geometric means of airborne nicotine were 0.74

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		mug/m(3) (GSD=4.05) in the smokers' homes, 0.13 mug/m(3) (GSD=2.4) in the e-cigarettes users' homes, and 0.02 mug/m(3) (GSD=3.51) in the control homes. The geometric means of salivary cotinine were 0.38 ng/ml (GSD=2.34) in the smokers' homes, 0.19 ng/ml (GSD=2.17) in the e-cigarette's users' homes, and 0.07 ng/ml (GSD=1.79) in the control homes. Salivary cotinine concentrations of the non-smokers exposed to e-cigarette's vapour at home (all exposed >= 2 h/day) were statistically significant different that those found in non-smokers exposed to second-hand smoke >= 2 h/day and in non-smokers from control homes. The results found that airborne markers were statistically higher in the homes of conventional combustible tobacco cigarette smokers (5.7 times higher) than in the homes of e-cigarette users. However, concentrations of both biomarkers among non-smokers exposed to conventional combustible tobacco cigarettes and to e-cigarette vapour were statistically similar (2 and 1.4 times higher, respectively). The authors concluded that non-smokers passively exposed to e-cigarettes absorb nicotine.[249] Device and products: Participants were considered exposed to aerosols from ENDS if they answered yes to one or both of the following questions: "During the past 30 days, were you in the same room with someone who was using electronic vapor products?"; "During the past 30 days, did you ride in a car with someone smoking electronic vapor products?"
Tackett et al.[251] 2019	Neither harm or benefit	The authors reported on a preliminary exploration of **second-hand smoke or vapour exposure in youth with sickle cell disease** through biochemical verification of cotinine, pulmonary functioning, and healthcare utilisation. Age: Thirty-one youth with Sex Sickle Cell (SC Type SS = 45.2%, mean age = 9.0 years; SD = 4.5 years) and their caregivers (mean age = 37.6 years; SD = 8.5 years) Sex: Child Gender Male 42% Female 58% Relationship to Child Mother 87% Country: USA Data source: Midwestern children's hospital. Population size: 31 parent-child dyads Data collection period: Not reported E-cigarette, smoking and other related status: Current and previous nicotine/tobacco use was assessed via self-report surveys. Caregivers reported past 30-day and previous or ever-use of tobacco. Caregivers who denied current cigarette use, but indicated past use were categorized as 'former smokers'; caregivers who reported current cigarette use were categorized as current smokers. Caregivers who answered 'no' to both questions were categorized as 'never smokers.' To assess household second-hand smoke exposure or second-hand 'vapor', caregivers reported how many individuals in the household smoked and/or used an electronic cigarette. A household SHS/SHVe variable was created by dichotomizing exposure as 'yes' or 'no.' Outcomes: pulmonary functioning, children over the age of six (N = 24) completed 5 trials of forced spirometry, all provided saliva for assessment of cotinine levels. Cotinine analyses indicated that 24 of the 27 participants (88%) were exposed, in some capacity, to second-hand smoke exposure (SHS)/ second-hand 'vapor'(SHVe). Interestingly, no childexhaled carbon monoxide values were elevated and only two caregivers (both self-identified as current smokers) were elevated, highlighting the variability of two different measures of second-hand smoke exposure and the benefit of

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers respiratory diseases
		utilizing salivary cotinine to measure second-hand smoke exposure / second-hand 'vapor' among children.[251] The authors concluded that the majority of youth (88%) were exposed to second-hand smoke via salivary cotinine. Interestingly, no significant associations were observed between youth cotinine levels and emergency department utilisation, physician-reported sickle cell crises, or pulmonary functioning. Present findings indicate a need to assess for second-hand smoke using objective assessment measures.[251] Device and products: Not reported

Table 71: Cross-sectional surveys papers on oral diseases, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		Oral health
Cho[252] 2017	Harm	The author reported on the relationship between **e-cigarette use and oral health**, measured as gingival pain and/or bleeding, tongue and/or inside-cheek pain, and cracked or broken teeth. Age: mean 15.0 (SD: 1.7). Sex: not reported for the subgroup reported in this paper. Country: South Korea Data source: Twelfth Korean Youth Risk Behaviour Web-based Survey Population size: 5,404 of 65,528 study participants. Data collection period: 2016 E-cigarette, smoking and other related status: E-cigarette users were grouped as use daily users, 0.5% (n = 297), '1 to 29 days past month users '1.9% (n = 1259) and former users 5.9% (n = 3848). Outcomes: 'gingival pain and/or bleeding', 'tongue and/or inside-cheek pain', and 'cracked or broken teeth' Outcome within the past 12 months were considered for analysis. Comparing 'daily e-cigarette users', '1 to 29 days past month e-cigarette users', and 'former e-cigarette users' with 'never e-cigarette users', the adjusted ORs for 'cracked or broken tooth' were 1.65 (95% CI: 1.19-2.27), 1.26 (95% CI: 1.06-1.51), and 1.16 (95% CI: 1.04-1.30) respectively. Comparing 'daily e-cigarette users' with 'never e-cigarette users', the adjusted OR for 'tongue and/or inside-cheek pain' was 1.54 (1.05-2.26). e-cigarette use among adolescents was not associated with 'gingival pain and/or bleeding' when adjusted for the potential confounders. The author reported that former e-cigarette users had a significantly higher occurrence of cracked or broken teeth than never e-cigarette users, and that daily e-cigarette users had a significantly higher occurrence of tongue and/or inside-cheek pain than never e-cigarette users, concluding that daily e-cigarette use among adolescents may be a risk factor for cracked or broken teeth and for tongue and/or inside-cheek pain.[252] Device and products: Not reported
Javed et al.[253] 2017	Harm	The authors reported on the relationship between cigarette smokers (group 1), individuals exclusively **vaping e-cigarettes** (group 2), and never-smokers (group 3) with **periodontal parameters and self-perceived oral symptoms**.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		Age: mean ages of 41.3 +/- 2.8 (former cigarette smokers), 37.6 +/- 2.1 (e-cigarette users), and 40.7 +/- 1.6 never-smokers) Sex: All male. Country: Saudi Arabia. Data source: participants were recruited from the outpatient department of the College of Dentistry, King Saud University, Riyadh, Saudi Arabia Population size: 94. Data collection period: June 2016 and February 2017. E-cigarette, smoking and other related status: Ninety-four male participants (N=33 group 1, N=31 group 2, and N=30 group 3). Group 1 Individuals who reported to have been smoking up to five cigarettes daily for at least 12 months were defined as former cigarette smokers. Group 2 e-cigarette users defined as individuals who were exclusively e-cigarette vaping at least once daily (one session) for 12 months. Group 3 participants who reported to have never used tobacco in any form were categorized as never-smokers Outcomes: Periodontal parameters: full-mouth plaque index, bleeding on probing, clinical attachment loss and probing depth >=4 mm measured at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, disto-lingual/palatal, mid-lingual/palatal, and mesio-lingual/palatal) on all maxillary and mandibular teeth, number of missing teeth, marginal bone loss. Self-perceived oral symptoms Plaque index (p<0.01) and probing depth ≥4 mm (p<0.01) were significantly higher in groups 1 and 2 than in group 3. Bleeding on probing was significantly higher in group 3 than in groups 1 and 2 (p<0.01). There was no difference in the number of missing teeth, clinical attachment loss, or marginal bone loss between all groups. Gingival pain was more often reported by individuals in group 1 than by individuals in groups 2 or 3 (p<0.01).[253] Device and products: Not reported
Akinkugbe et al.[254] 2018	Harm	The authors investigated associations between self-reported use of cigarettes and **e-cigarettes with oral health status.** Age: 6,997 aged 12 to 14 years and 6,653 aged 15 to 17 years Sex: 6,993 males, 6,657 females Country: USA. Ethnicity: 9,471. white, 2,086 Black 2,093 Other Data source: Population Assessment of Tobacco and Health study Population size: 13,650. Data collection period: 2013-2014 E-cigarette, smoking and other related status: Ever cigarette use, ever e-cigarette use. Adolescents were asked if they have ever tried cigarette smoking (i.e., conventional cigarette smoking), even 1 or 2 puffs (yes vs. no; defined in this study as ever use) or at least 1 or 2 puffs in the last 30 days (yes vs. no; defined in this study as current use). Past 30-day use of tobacco products among adolescents is a standard measure to indicate current use. Similar questions were elicited for e-cigarette use and defined in this study as ever use, if they have ever tried vaping e-cigarettes, and current use if they had used e-cigarettes in the past 30 days. Outcomes: past-year diagnoses with dental problems by a doctor, dentist, or other health professional (self-reported by parent or emancipated youth). Specifically, such as dental health issues such as cavities, gum disease or dental stains. The authors used adjusted logistic regression to estimate prevalence odds ratios (PORs) and 95% CIs. Self-reported provider-diagnosed dental problems'

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		covariate-adjusted values were: POR: 1.50 (95% CI: 1.18–1.90) in current cigarette users and POR: 1.11 (95% CI: 0.79–1.55) in current e-cigarette users. Ever use of cigarettes and e-cigarettes was likewise associated with increased prevalence odds of self-reported past-year diagnosis of dental problems, although to a lesser magnitude. The authors concluded that dual use of e-cigarettes and conventional combustible tobacco cigarettes is associated with poor oral health outcomes among adolescents.[254] Device and products: Not reported
Al-Aali et al.[255] 2018	Harm	The authors reported on the relationship between **vaping e-cigarettes and never smoking** with clinical and radiographic **peri-implant parameters** and levels of tumor necrosis factor alpha (TNF-alpha) and interleukin (IL)-1beta. Age: Mean age SD (in years) Vaping Individuals 35.8+/-6.2 Never Smokers 42.6+/-2.7. Sex: 92 males. Country: Saudi Arabia Data source: recruited from specialist prosthodontic private practice Population size: 92. Data collection period: January 2016 and March 2017 E-cigarette, smoking and other related status: The study population consisted of 47 individuals vaping e-cigarettes (group-1) and 45 non-smokers (group-2). Group 1: current vapers who reported vaping e-cigarettes for at least the past year; (b) group 2: participants who never consumed tobacco in any form during their life time Outcomes: peri-implant plaque index (PI), bleeding on probing (BOP), probing depth (PD) and peri-implant bone loss (PIBL), in addition to levels of TNF-alpha and IL-1beta in peri-implant sulcular fluid Bleeding on probing showed statistically significantly higher values in group-2 patients as compared to group-1 patients (P < .01). Probing depth >= 4 mm and peri-implant bone was statistically significantly higher in group-1 patients as compared to group-2 patients (P < .05). Mean concentrations of TNF-alpha (P < .001) and IL-1beta (P < .01) were statistically significantly increased in individuals in group 1 as compared with group 2. There was a significant positive correlation between TNF-alpha levels and bleeding on probing (P = .02) The authors concluded that clinical and radiographic peri-implant parameters were compromised among vaping individuals. The authors concluded that increased levels of proinflammatory cytokines in peri-implant sulcular fluid may suggest greater local inflammatory response in vaping individuals for peri-implant inflammation and peri-implant bone loss (p=0.016). A significant positive correlation was found between IL-1 beta and peri-implant bone loss (p=0.018) in e-cigarette users compared to non-users of e-cigarettes and conventional combustible tobacco cigarettes.[255] Device and products: Not reported
AlQahtani et al.[256] 2018	Harm	The authors reported on the relationship of water pipe smokers, **e-cigarette users**, and cigarette smokers with **peri-implant parameters and local levels of proinflammatory cytokines**; specifically, periodontal and peri-implant plaque index, bleeding on probing, and **probing depth** (≥4 mm) and **levels of TNF-alpha,** interleukin **-6**, and interleukin **-1 beta** in peri-implant sulcular fluid. Age: mean age 41.8 (34-53 years). Sex: All male. Country: Saudi Arabia Data source: Population size: 160. Data collection period:

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		E-cigarette, smoking and other related status: 40 cigarette smokers, 40 waterpipe smokers (aka hookah, sheesha), 40 subjects using e-cigarettes , and 40 non-smokers who reported to smoke at least 10 cigarettes daily for at least more than 5 years; (c) non-smokers who never smoked tobacco; and (d) ≥1 dental implant(s) in service for ≥3 years Cigarette smoking was smoked at an average of 15 times daily with a mean duration of 8 minutes, 6 times daily for waterpipe smokers at a mean duration of 31.6 minutes, and 6.5 times daily for subjects using e-cigarettes at an average of 37.7 minutes Outcomes: peri-implant parameters and local levels of proinflammatory cytokines, specifically periodontal and peri-implant plaque index (PI), bleeding on probing (BOP), and probing depth (PD >= 4 mm) and levels of tumour necrosis factor-alpha (TNF-alpha), interleukin (IL)-6, and IL-1beta in peri-implant sulcular fluid Mean peri-implant plaque index (p<0.05), probing depth ≥4 mm (p<0.05), and total radiographic bone loss (p<0.01) were significantly higher among cigarette smokers, water pipe smokers, and subjects using e-cigarettes compared with non-smokers. Statistical differences in bleeding on probing were observed in non-smokers (p<0.01) compared to cigarette smokers, water pipe smokers, and subjects using e-cigarettes. Cigarette smokers and water pipe smokers showed significantly higher probing depth ≥4 mm and radiographic bone loss compared with subjects using e-cigarettes (p<0.05). Levels of TNF-alpha, IL-6, and IL-1 beta were significantly higher in cigarette smokers, water pipe smokers, and subjects using e-cigarettes compared to non-smokers. There were no statistical differences in the mean levels of all proinflammatory cytokines among individuals who were cigarette smokers or water pipe smokers.[256] Device and products: Not reported
Mokeem et al.[260] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between cigarette smoking, water pipe smoking**, e-cigarette** using, and never smoking behaviours, and outcome **oral health measures** of clinical (plaque index, bleeding on probing, probing pocket depth, and clinical attachment loss), radiographic (marginal bone loss), and periodontal parameters, and of whole salivary cotinine, interleukin -1 beta, and interleukin -6 levels. Age: (mean ± SD) 42.4 ± 5.6 Cigarette -smokers 44.7 ± 4.5 Waterpipe-smokers 28.3 ± 3.5 e-cigarette users 40.6 ± 4.5 Never-smokers Sex: All males. Country: Saudi Arabia. Data source: Not specified Population size: 154. Data collection period: Not specified E-cigarette, smoking and other related status: 39 cigarette-smokers, 40 waterpipe-smokers, 37 e-cigarette users and 38 never-smokers. Individuals that reported to be smoking at least 5 cigarettes daily for at least 12 months were defined as “cigarette-smokers”. “Waterpipe smokers” were defined as individuals who reported smoking waterpipe at least once a day for a minimum duration of 12-months. “E-cigarette users” were defined as individuals vaping exclusively e-cigarettes for at least 12 months and had never used smoked tobacco in the past. Individuals who reported to have never smoked tobacco and/or consumed smokeless tobacco products were defined as “Never-smokers” Outcomes: clinical (plaque index [PI], bleeding on probing [BOP], probing pocket depth [PPD], clinical attachment loss [CAL]), radiographic (marginal bone loss [MBL]) periodontal parameters, whole salivary cotinine, interleukin (IL)-1beta and IL-6 levels.

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		Full mouth plaque index, bleeding on probing, probing pocket depth and clinical attachment loss were measured on all teeth (excluding third molars); and marginal bone loss was measured in digital intra-oral radiographs. Unstimulated whole salivary flow rate (UWSFR) and whole salivary cotinine, IL-1beta and IL-6 levels were also measured. Group comparisons were performed using one-way analysis of variance and Bonferroni post-hoc tests. There was no difference in unstimulated whole salivary flow rate among the groups. Cotinine levels were significantly higher among cigarette- (P<0.001) and waterpipe-smokers (P<0.001) and E-cigarette users (P<0.001) than never-smokers. IL-1beta (P<0.01) and IL-6 (P<0.01) levels were significantly higher among cigarette- and waterpipe-smokers than e-cigarette users and never-smokers. There was no difference in PPD, CAL, mesial and distal MBL and whole salivary IL-1beta and IL-6 levels among e-cigarette users and never-smokers. The authors reported that clinical and radiographic parameters of periodontal inflammation were poorer in cigarette and water pipe smokers than in e-cigarette users and never-smokers, and that whole salivary cotinine levels were similar in all groups. Whole salivary interleukin -1 beta and interleukin -6 levels were higher in cigarette and water pipe smokers than e-cigarette users and never-smokers.[260] Device and Products: Not reported
Alqahtani *et al.*[265] 2019	Harm	The authors compared **cotinine levels** in the **peri-implant sulcular fluid** among cigarette and water pipe smokers, **e-cigarette users**, and non-smokers. Age mean (SD) years: Cigarette smokers 36.3 ± 1.2 Waterpipe smokers 34.1 ± 1.4 Electronic-cigarette users 33.5 ± 0.7 Nonsmokers 32.2 ± 0.6 Sex: All males. Country: Saudi Arabia Data source: Partially edentulous adults rehabilitated with dental implant were included. Every individual among the study groups had one dental implant placed in the region of a missing maxillary or mandibular premolar or molar. The dental implants were in function since 1.6 ± 0.4, 1.3 ± 0.2, 1.4 ± 0.2, and 1.3 ± 0.2 years in cigarette smokers, waterpipe smokers, electronic cigarette users, and nonsmokers, respectively. Population size: One hundred two male individuals 35 cigarette smokers, 33 waterpipe smokers, 34 e-cigarette users, and 35 non-smokers[265] Data collection period: Not reported E-cigarette, smoking and other related status: 35 cigarette smokers, 33 waterpipe smokers, 34 e-cigarette users, and 35 non-smokers. Cigarette smokers, waterpipe smokers, and e-cigarette users were using their nicotinic products for 10.2 ± 4.1, 8.3 ± 0.4, and 3.5 ± 0.6 years, respectively. Cigarette smokers were smoking 9.2 ± 0.6 cigarettes daily, and waterpipe smokers were using waterpipe 5.1 ± 0.3 times daily. Electronic-cigarette users were vaping 14.3 ± 1.2 times daily. Cigarette and waterpipe smokers were unaware of the amount of nicotine present in their respective tobacco products; and the amount of nicotine present in the e-liquids used by electronic cigarette users was 8.4 ± 0.6 mg. The mean duration of each session of cigarette and waterpipe smoking among the representative groups were 6.6 ± 0.5 and 16.3 ± 2.4 minutes, respectively. Electronic-cigarette users were vaping for a mean duration of 5.1 ± 0.6 minutes during each session of vaping. All waterpipe smokers and e-cigarette users were former cigarette smokers who had quit smoking cigarettes 8.3 ± 0.4 and 3.5 ± 0.6 years ago, respectively. Outcomes: Cotinine levels in peri-implant sulcular fluid

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		The authors concluded that habitual use of nicotinic products enhances the expression of cotinine in the peri-implant sulcular fluid. Cotinine levels in the peri-implant sulcular fluid of cigarette and water pipe smokers and e-cigarette users are comparable.[256] Device and products: Not reported
ArRejaie *et al.*[261] 2019	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between cigarette smokers', **e-cigarette vaping** individuals', and non-smokers' **peri-implant health** using clinical and radiographic peri-implant parameters (specifically peri-implant plaque index, bleeding on probing, probing depth, and marginal bone loss), levels of matrix metalloproteinase-9, and interleukin -1 beta levels. Age: Cigarette smokers 40.4 ± 3.5 Vaping individuals 35.8 ± 6.2 Non-smokers 42.6 ± 2.7. Sex: All male. Country: Saudi Arabia Data source: Attendees at the Department of Prosthetic Dental Sciences, King Saud University Population size: 95. Data collection period: June 2016 to September 2017. E-cigarette, smoking and other related status: Thirty-two cigarette smokers (group 1), 31 individuals vaping e-cigarettes (group 2), and 32 non-smokers (group 3) were included Outcomes: clinical and radiographic peri-implant parameters (specifically peri-implant plaque index (PI), bleeding on probing (BOP), probing depth (PD) and marginal bone loss (MBL)), levels of matrix metalloproteinase (MMP)-9 and interleukin (IL)-1beta levels. Bleeding on probing showed significantly higher values in non-smokers (group 3) as compared with cigarette smokers (group 1) and vaping e-cigarettes (group 2) ($P < 0.01$). Peri-implant plaque index ($P < 0.01$), probing depth >= 4 mm ($P < 0.01$), and mean concentrations of matrix metalloproteinase -9 ($P < 0.001$) and IL-1beta ($P < 0.01$) were significantly higher in groups 1 and 2 than group 3. Marginal bone loss was significantly higher in group 1 as compared with group 2 and group 3 ($P < 0.01$). Significant positive correlations were found between matrix metalloproteinase-9 ($P = 0.0198$) and IL-1beta ($P = 0.0047$) levels and Marginal bone loss in group 1; and a significant positive correlation between IL-1beta and MBL in group 2 ($P = 0.0031$). The authors concluded that peri-implant health was more compromised among cigarette smokers than vaping individuals and non-smokers. Increased levels of proinflammatory cytokines in cigarette smokers and vaping individuals may suggest greater peri-implant inflammatory response. response[261] Device and products: Not reported
Huilgol et al.[259] 2019	Harm	The authors reported on the relationship between **e-cigarette use,** defined as daily or intermittent use within 30 days prior to survey administration, and **poor oral health** (the number of permanent teeth removed due to non-traumatic causes). Age: 18 to 65 years plus Sex: Male and Female. Numbers for total survey population only reported Country: USA. Ethnicity: White Black Asian Other. Data source: Behavioural Risk Factor Surveillance System Population size: 67 003 (14.8%) of the original sample (456 343) reported current smoking within the previous 30 days, only 4957 (1.1%) reported current daily use of e-cigarettes, 10 062 (2.2%) reported intermittent use of e-

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		cigarettes, and 14 948 (3.3%) reported current use of smokeless tobacco. Numbers for total survey population only reported. Data collection period: 2016 E-cigarette, smoking and other related status: e-cigarette use, was determined on a 4-level smoker status within 30 days prior to survey administration (everyday e-cigarette user, someday e-cigarette user, former e-cigarette user and non-e-cigarette user). Cigarette smoking status was categorized into current smokers and non/former smokers. Smokeless tobacco use was defined by chewing tobacco, snuff or snus, and was classified into everyday/intermittent users and non-users. Outcomes: number of permanent teeth removed due to non-traumatic causes In multivariable analysis, daily e-cigarette use was independently associated with 78% higher odds of poor oral health (AOR: 1.78; 95% CI: 1.39–2.30; *p*<0.001). The authors concluded that daily, but not intermittent, use of e-cigarettes was independently associated with poor oral health.[259] Device and products: Not reported
Jeong et al.[257] 2020	Harm	The authors reported on the association of conventional combustible tobacco cigarette smoking and **e-cigarette vaping with periodontal disease.** Age mean (SD) years: 19 years of age plus. Sex: 5,715 males, 7,836 females. Country: South Korea Data source: Korean National Health and Nutrition Examination Survey Population size: 13,551. Data collection period: 2013 to 2015 E-cigarette, smoking and other related status: e-cigarettes vapers, conventional tobacco cigarettes smokers, ex-users, and non-users Outcomes: Periodontal status was measured by the Community Periodontal Index. 187 men and 35 women who vape electronic cigarette, 67 (35.8%) men and 10 (28.6%) women had periodontal diseases. Out of 1,957 men and 363 women who smoke conventional tobacco cigarettes, 861 (44.0%) men and 121 (35.3%) women had periodontal diseases. Periodontal disease was more prevalent in each vapers and smokers than non-users in men (e-cigarettes: odds ratio [OR] = 2.34, 95% confidence interval [CI] = 1.52 to 3.59, conventional tobacco cigarettes: OR = 2.17, 95% CI = 1.76 to 2.68) The authors concluded that e-cigarette and conventional combustible tobacco cigarette use were both significantly associated with increased periodontal disease rates. After adjusting for demographic, socioeconomic, and health-related characteristics, both vaping and smoking had a significant association with periodontal diseases. The authors suggested that vaping may not be a safe alternative to smoking.[257] Device and products: Not reported
Vora et al.[258] 2019	Harm	The authors reported on the relationship between smoking behaviours – specifically cigarette smoking and using other types of **tobacco products – and self-reported gingival disease.** Age: > 18 years of age. Sex: male and females. Country: USA Data source: Population Assessment of Tobacco and Health study Population size: 32,320. Data collection period: 2013-2014

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		E-cigarette, smoking and other related status: tobacco never users, pipe users, -cigarette users, multiple tobacco product users, recent quitters, Outcomes: Self-reported gingival disease diagnosis. Groups with the highest adjusted relative odds for diagnosis (reference, lifetime tobacco never users) were pipe users (2.7; 95% confidence interval [CI], 1.3 to 5.3), e-cigarette users (2.9; 95% CI, 1.9 to 4.5), multiple tobacco product users (2.8; 95% CI, 2.4 to 3.4), and recent (< 12 months) quitters (2.8; 95% CI, 2.0 to 3.8). The authors concluded that numerous tobacco use patterns were associated with worse periodontal health compared with tobacco never users.[258] Device and products: Not reported
		Markers of infection
Stewart[264] 2018	Neither harm or benefit	The author reported the effects of tobacco smoke and **e-cigarette vapour** exposure on the **oral and gut microbiota** in humans. Age median (interquartile range): Controls 31 (28–36), E-cigarette 29 (24–37), Tobacco smoke 35 (30–45). Sex: 29 males, 2 females. Country: USA. Ethnicity: varied by group but included White Hispanic Asian Black. Data source: All participants were recruited from the Houston area Population size: 30 individuals in three distinct exposure groups; e-cigarette users (n = 10), tobacco smokers (n = 10), and matched controls (n = 10). Data collection period: Not reported E-cigarette, smoking and other related status: E-cigarettes users Nicotine concentration (mg), median (interquartile range) 9 (6–12) Outcomes: DNA was extracted from 125 mg of fresh faecal sample, DNA from buccal swabs and saliva samples was also assessed, The bacterial 16S rRNA gene V4 region. Faces had a distinct bacterial profile compared to the oral samples (buccal swab and saliva). The author concluded that people who regularly use e-cigarettes do not have measurably different oral or gut bacterial communities compared to non-smokers.[264] Device and products: Not reported
Cichonska et al.[262] 2019	Harm	The authors reported on the relationship between **e-cigarettes** and **selected antibacterial properties of saliva** (IgA, lysozyme, and lactoferrin levels). Age mean (SD) years: 20 to 30 years. Sex: Not reported Country: Poland Data source: students of Medical University of Gdansk and young patients, who volunteered for a follow-up examination of periodontium and oral mucosa at the Department of Periodontology and Oral Mucosa Diseases Population size: 120 patients. 40 users of e-cigarettes, 40 smokers of conventional combustible tobacco cigarettes and 40 non-smokers Data collection period: E-cigarette, smoking and other related status: 40 users of e-cigarettes, 40 smokers of conventional combustible tobacco cigarettes and 40 non-smokers. E-cigarette users were using e-cigarettes with small nicotine concentration for minimum 6 months vaping at least 50 times per day. Conventional combustible tobacco cigarette smokers were smoking at least 10 cigarettes

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers oral diseases
		per day for a minimum of 6 months. There were no group of patients smoking both traditional and e-cigarettes. Outcomes: IgA, lysozyme and lactoferrin levels on unstimulated saliva The authors concluded that the saliva of e-cigarette users showed changes in antibacterial properties in comparison with the control group and with conventional combustible tobacco cigarette smokers. More specifically, among e-cigarette users, statistically significant differences were observed in levels of lysozyme and lactoferrin; however, no statistically significant differences for the IgA levels were found.[262] Device and products: Not reported
Mokeem et al.[263] 2019	Harm	The authors reported on the relationship between **oral *Candida albicans* carriage**, number of missing teeth, and unstimulated whole salivary flow rate with smoking-related behaviours, specifically among cigarette and water pipe smokers, **e-cigarette users**, and never-smokers. Age: Mean age in years (SD) Group-1 33.2 ± 8.6 Group-2 36.3 ± 6.9 Group-3 29.4 ± 4.5 Group-4 32.5 ± 5.4 Sex: All male. Country: Saudi Arabia Data source: The outpatient department of a local University-based dental clinic in Riyadh, Saudi Arabia Population size: 129 male individuals (34, 33, 30, and 32 in groups 1, 2, 3, and 4, respectively) were included. Data collection period: April 2017 and January 2018 E-cigarette, smoking and other related status: 34 cigarette-smokers (Group-1), 33 waterpipe-smokers (Group-2), 30 e-cigarette users (Group-3), and 32 never-smokers (Group-4). In groups 1 and 2, mean durations of cigarette and waterpipe smoking were comparable. Outcomes: Oral Candida carriage, number of missing teeth and unstimulated whole salivary flow rate (UWSFR) The authors concluded that oral *Candida albicans* carriage was significantly higher among cigarette and water pipe smokers and e-cigarette users than among never-smokers. No significant differences were identified among groups in the oral carriage of other Candida species.[263] Device and Products: Not reported

Table 72: Cross-sectional surveys papers on exposure to e-cigarette toxins, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
Hecht *et al.*[267] 2015	Harm, but less harmful than tobacco cigarettes	The authors reported on the **relationship between e-cigarette** smokers who had not smoked tobacco cigarettes for at least 2 months and the presence of **a suite of toxicant and carcinogen metabolites**, including: 1-hydroxypyrene (1-HOP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), 3-hydroxypropylmercapturic acid (3-HPMA), 2-hydroxypropylmercapturic acid (2-HPMA), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), S-phenylmercapturic acid (SPMA), nicotine, and cotinine. Age: years (SD) e-cigarette users 34.0 ± 12.7 Cigarette smokers: Carmella et al 43.3 ± 10.8, Hatsukami *et al.* 41.3 ± 13.2, Zarth et al 34.4 ± 9.5

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		Sex: Female percentages in each study group were: 42.9% Carmella et al 64.7%, Hatsukami *et al.* 47.3%, Zarth et al 57.5% Country: USA Data source: Subjects were recruited by a member of the research staff of the University of Minnesota Tobacco Research Programs and initially screened over the telephone. Population size: 28. Data collection period: Not reported E-cigarette, smoking and other related status: Of the 28 participants eligible for this analysis, e-cigarette use was for a median of 9 months (range 3–36) and they quit smoking 9 months (range 2–36) before study entry. Most used e-cigarettes daily (96.2%) and the average nicotine concentrations were 12.5 ± 7.0 mg/ml. All e-cigarette users used refillable e-cigarettes and refilled an average of one time (range 0.3–5) per day. The brands of e-cigarettes used (number) are: Aqua (2) Aspire (2) Buck Naked Express (1) eGo (8) eQ (1) Green Smoke (1) Green Smart Living (1) Hades (1) iGo (1) Itazte (5) JDTech (1) Kanger (7) MyVape (1) Origin (1) Provari (4) Sigelei (1) SMOKTech (2) V2 (1) Vapor4Life (1) Vision Spinner (3) Vmax (1). aSome users used more than one brand. bTwo subjects used cartridges (Green Smoke, V2, and Green Smart Living); all others used tank systems. The 222-comparison group consisted of smokers who wanted to quit and represented, 17 smokers, 165 smokers of "light" cigarettes, and 40 cigarette smokers from three different study groups. Outcomes: the authors quantified urinary toxicant and carcinogen metabolites in people using e-cigarettes and compared their levels to those found in cigarette smokers. The compounds quantified were 1-hydroxypyrene (1-HOP), a biomarker of carcinogenic PAH exposure; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), metabolites of the tobacco-specific nitrosamine and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK); 3-hydroxypropylmercapturic acid (3-HPMA), a metabolite of the toxicant acrolein; 2-hydroxypropylmercapturic acid (2-HPMA), a metabolite of the carcinogen propylene oxide; 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), a metabolite of the carcinogen crotonaldehyde; S-phenylmercapturic acid, a metabolite of the carcinogen benzene; and nicotine and cotinine. Comparisons of findings in the primary studies e-cigarette smokers were made with findings obtained from previous analyses of cigarette smokers' urine using essentially identical assay methods in three previous studies. In one study, 17 smokers who wanted to quit were recruited and provided urine samples at baseline prior to 8 weeks of refraining from smoking; baseline data were used here. A second study recruited 165 smokers of "light" cigarettes who were interested in quitting smoking and were assigned to either low nicotine cigarettes or nicotine lozenges; their baseline first morning urine samples were analysed for the data reported here. The third study analysed 40 samples from cigarette smokers who provided spot urine samples to the Tobacco Research Programs Repository. Levels of 1-HOP, total NNAL, 3-HPMA, 2-HPMA, HMPMA, and SPMA were significantly lower in the urine of e-cigarette users compared with that of cigarette smokers. Levels of nicotine and cotinine were significantly lower in e-cigarette users compared with cigarette smokers in one study, but not in another. The authors concluded, with respect to the compounds analysed in this study, that e-cigarettes have a more favourable toxicity profile than tobacco cigarettes.[267]

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		Device and products: All e-cigarette users used refillable e-cigarettes and refilled an average of one time (range 0.3–5) per day. The brands of e-cigarettes used are: Aqua, Aspire, Buck Naked Express, eGo, eQ, Green Smoke*, Green Smart Living*, Hades, iGo, Itazte, JDTech, Kanger, MyVape, Origin, Provari, Sigelei, SMOKTech, V2*, Vapor4Life, Vision Spinner and Vmax. Two subjects used cartridges (*Green Smoke, *V2, and *Green Smart Living); all others used tank systems. Some users used more than one.
Aherrera et al.[272] 2017	Harm	The authors reported on the relationship between **e-cigarettes** and **the metals nickel and chromium, which are components of the devices' heating coil.** Age: 18 years of age or older. Sex: Not reported. Country: USA. Data source: E-cigarette users were recruited through vaping conventions, flyers posted in universities, and e-cigarette shops Population size: 59 of 64. Data collection period: December 2015 and March 2016 E-cigarette, smoking and other related status: 50 sole users (never smokers or had quit smoking at least 3 months prior) and 14 dual users (used combustible cigarettes at least weekly) participants were daily e-cigarette users, and users for at least 6 weeks. Outcomes: Urine, saliva, exhaled breath condensate levels of nickel (Ni) and chromium The authors concluded that the study of daily e-cigarette users indicates that metals in e-cigarette aerosol are inhaled and absorbed into the bodies of users, representing a relevant contributor to metal internal dose. As the first study to make direct comparisons between source and metal biomarkers from e-cigarette use, the authors found that nickel in urine and saliva and chromium in saliva were positively associated with concentrations of the corresponding metals in aerosol samples collected from users' personal vaping devices, providing strong evidence that metals present in the aerosol are inhaled by the user. E-cigarette use patterns – such as more e-liquid consumed per week, a shorter time between waking and first vape, and a higher voltage used – were also associated with higher nickel biomarker levels. Device and products: According to device type, 5 participants used first-generation devices (cigalikes), while 59 used 2nd or 3rd generation devices that operate using a customizable tank-like system and/or mechanical mods (modified e-cigarettes). Data on e-liquid consumed per week, time to first vape from waking in the morning, preferred voltage, heating coil used (Kanthal/Nichrome/other), coil change per month, and nicotine concentrations in e-liquid was gathered. Data on e-liquid consumption per week (tertiles), time to first vape from waking (within 15 / more than 15 min), preferred voltage for e-cigarette use (tertiles), coil change per month (1–2 / 3 times or more per month), and urinary cotinine (tertiles), as well as the corresponding metal levels in samples obtained from the dispenser, aerosol, and tank (tertiles) were gathered. Analyses were restricted to users of tank-style/mods devices (n = 59), as information on coil change and e-liquid consumed, and collection of e-liquid from the dispenser and/or tank did not apply to cigalike devices. Median Nickel and chromium level were 0.73 and 0.39mug/g in urine, 2.25 and 1.53mug/L in saliva, and 1.25 and 0.29mug/L in exhaled breath condensate. Increasing tertiles of e-liquid consumption per week tended to be associated with higher urinary, saliva and EBC Ni levels. In fully adjusted models the association was only statistically significant for the second tertile of e-liquid per week and saliva Ni (GMR 2.88, 95%CI 1.11, 7.51).

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		Participants who vaped within 15 min from waking had 79% (95%CI 1.14, 2.82) higher urine Ni levels compared to those taking longer to vape. By self-reported voltage, there was a non-statistically significant trend with higher urine Ni levels (p for trend 0.14); with saliva, the association was only observed for the second tertile (4.06–4.47 V) (GMR 3.65, 95%CI 1.47, 9.07). Changing coils ≥3 times per month was associated with 91% (95%CI 1.23, 2.98) higher urinary Ni levels. Tertiles 2 and 3 of urinary cotinine were associated with 38% and 80% higher urinary Ni levels (p-trend 0.04), respectively. Ni levels in e-cigarette dispenser samples were not associated with any of the Ni biomarkers. For Cr biomarkers, the two highest compared to the lowest tertile of liquid consumption per week were associated with 28% and 71% higher levels in EBC (p-trend 0.08), 21% and 56% higher levels in saliva (p-trend 0.26), and 14% and 30% higher levels in urine (p-trend 0.29). Cr levels in dispenser samples were not associated with Cr biomarkers.[272]
Badea et al.[266] 2018	Harm	The authors reported on the relationship between non-smokers, cigarette smokers, and **e-cigarette users** with the presence of a **range of inorganic elements**. Serum concentration levels of 43 elements, including trace elements and other rare earth elements and minor elements considered pollutants were measured. Age: years (SD) Non-smokers 24.5+/- 6.7, Cigarette smokers 28.4 +/- 10.8, E-cigarette users male 35.2 +/- 9.4 Sex: Non-smokers male n= 10 female n=48, Cigarette smokers male n= 17 female, n=41 E-cigarette users male n=8 female n=26 Country: Brasov (Romania) Data source: convenience sample Population size: 150 Data collection period: December 2017 and February 2018 E-cigarette, smoking and other related status: 58 non-smokers, 58 conventional cigarette smokers, and 34 e-cigarette users Outcomes: concentration of 42 of the (current) 275 elements, including trace elements, in the Agency for Toxic Substances and Disease Registry (ATSDR's) priority pollutant list and rare earth elements were measured by ICP-MS in the blood serum of participants. The full list consisted of: six trace elements (Chromium was excluded from the analyses): u (copper), Fe (iron), Mn (manganese), Mo (molybdenum), Se (selenium), Zn (zinc); 17 ATSDR's priority pollutant list elements: Ag (silver), As (arsenic), Ba (barium), Be (beryllium), Cd (cadmium), Co (cobalt), Hg (mercury), Ni (nickel), Pb (lead), Pd (palladium), Sb (antimony), Sn (tin), Sr (strontium), Th (thorium), Tl (thallium), U (uranium),V (vanadium), and 29 lanthanides and other rare earth elements (REE): Ce (cerium), Dy (dysprosium), Er (erbium), Eu (europium), Ga (gallium), Gd (gadolinium), Ho (holmium), In (indium), La (lanthanum), Lu (lutetium), Nb (niobium),Nd (neodymium), Pr (praseodymium), Sm (samarium), Ta (tantalum),Tb (terbium), Tm (thulium), Y (yttrium),Yb (ytterbium), Σ lanthanides. The authors concluded that tobacco smoke is a source of toxic elements such as copper, zinc, antimony, strontium, and vanadium, and that e-cigarettes seem to be a new source for intake of silver, tin, and rare earth elements such as cerium, erbium, and gadolinium.[266] Device and products: Not reported

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
Goniewicz et al.[268] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on estimates of biomarker concentrations in combustible cigarette users, **e-cigarette users**, dual users, and never tobacco users of **tobacco-related toxicant concentrations**. Age: most were aged 35 to 54 years. Sex: women (weighted percentage, 60%; 95%CI, 59%-62%), Country: USA. Data source: Population Assessment of Tobacco and Health study Population size: 5,105. Data collection period: November 2016 to October 2017 E-cigarette, smoking and other related status: (n = 247) current exclusive e-cigarette users, (n = 2,411) current exclusive cigarette smokers, (n = 792) users of both products (dual users) compared with (n = 1655) never tobacco users. The analysis consisted of current product users, all of whom reported (1) current every day or some-days use of cigarettes, e-cigarettes, or both products; (2) no current (every day or some-days use) use of any other tobacco products; and (3) no use of nicotine replacement therapies in the past 3 days. In addition, cigarette-only smokers and dual users had to report smoking at least 100 cigarettes in their lifetime to be included. Comparison were made between current cigarette and e-cigarette users with never users who reported no lifetime tobacco use. Outcomes: 50 individual biomarkers from 5 major classes of tobacco product constituents were measured. Specifically, nicotine, tobacco-specific nitrosamines (TSNAs), metals, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs). urinary nicotine metabolites specifically nicotine (internal biomarker tne2); tobacco-specific nitrosamines (tsnas) 4-(methylnitros-amino)- 1-(3-pyridyl)- 1-butanone; metals, lead cadmium; polycyclic aromatic hydrocarbons (pahs) naphthalene, pyrene, and volatile organic compounds (vocs) acrylonitrile, acrolein acrylamide. The complete list of biomarkers are: Urinary Nicotine Metabolites: trans‐3’‐Hydroxycotinine (HCTT), Cotinine (COTT), Nicotine (NICT), Cotinine N‐oxide (COXT), Nicotine 1’‐oxide (NOXT), Norcotinine (NCCT), Nornicotine (NNCT) Minor Tobacco Alkaloids: Anabasine (ANBT), Anatabine (ANTT); Arsenic and Arsenic Compounds: Arsenous Acid, Arsenic Acid, Dimethylarsinic acid, Monomethylarsonic acid Tobacco Specific Nitrosamines: 4‐methylnitrosamino)‐4‐(3‐pyridyl)‐1‐butanol (NNAL), N’‐nitrosonornicotine (NNN), N’‐nitrosoanatabine (NAT), N’‐nitrosoanabasine (NAB) Metals: Beryllium (UBE), Cadmium (UCD), Cobalt (UCO), Manganese (UMN), Lead (UPB), Strontium (USR), Thallium (UTL), Uranium (UUR); Polycyclic Aromatic Hydrocarbons: 1‐Naphthol or 1‐hydroxynaphthalene (1‐NAP), 2‐Naphthol or 2‐hydroxynaphthalene (2‐NAP), 3‐Hydroxyfluorene (3‐FLU), 2‐Hydroxyfluorene (2‐FLU), 1‐Hydroxyphenanthrene (1‐PHE), 1‐Hydroxypyrene (1‐PYR), 2‐Hydroxyphenanthrene and 3‐Hydroxyphenanthrene (2‐3PHE) Volatile Organic Compounds (VOCs): 2‐Methylhippuric acid (2MHA) (Xylene), 3, 4‐Methylhippuric acid (34MH) (Xylene), N‐Acetyl‐S‐(2‐carbamoylethyl)‐L‐cysteine (AAMA) (Acrylamide), N‐Acetyl‐S‐(N‐methylcarbamoyl)‐L‐cysteine (AMCA) (N, NDimethylformamide/isocyanates), N‐Acetyl‐S‐(benzyl)‐L‐cysteine

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		(BMA) (Toluene), N - Acetyl - S - (2 - carboxyethyl) - L - cysteine (CEMA) (Acrolein), N - Acetyl - S - (1 - cyano - 2 - hydroxyethyl) - L - cysteine (CYHA) (Acrylonitrile), N - Acetyl - S - (2 - cyanoethyl) - L - cysteine (CYMA) (Acrylonitrile), N - Acetyl - S - (3,4 - dihydroxybutyl) - L - cysteine (DHBM) (1,3 - Butadiene), N - Acetyl - S - (2 - carbamoyl - 2 - hydroxyethyl) - L - cysteine (GAMA) (Acrylamide), N - Acetyl - S - (2 - hydroxyethyl) - L - cysteine (HEMA) (Acrylonitrile, vinyl chloride, ethylene oxide), N - Acetyl - S - (2 - hydroxypropyl) - L - cysteine (HPM2) (Propylene Oxide), N - Acetyl - S - (3 - hydroxypropyl) - L - cysteine (HPMA) (Acrolein), N - Acetyl - S - (3 - hydroxypropyl - 1 - methyl) - L - cysteine (HPMM) (Crotonaldehyde), N - Acetyl - S - (4 - hydroxy - 2 - methyl - 2 - buten - 1 - yl) - L - cysteine (IPM3) (Isoprene), Mandelic acid (MADA), N - Acetyl - S - (4 - hydroxy - 2 - buten - 1 - yl) - L - cysteine (MHB3) (1,3 Butadiene), Phenylglyoxylic acid (PGHA) (Ethylbenzene, styrene), N - Acetyl - S - (phenyl) - L - cysteine (PMA) (Benzene), 2 - Thioxothiazolidine - 4 - carboxylic acid (TTCA) (Carbon Disulfide). This study examined 50 biomarkers associated with exposure to tobacco. Participants included adults who provided a urine sample and data on tobacco use. Geometric mean concentrations of 50 individual biomarkers from 5 major classes of tobacco product constituents were measured: specifically, nicotine, tobacco-specific nitrosamines (TSNAs), metals, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs). Compared with exclusive e-cigarette users, never users had 19% to 81% significantly lower concentrations of biomarkers of exposure to nicotine, tobacco-specific nitrosamines, some metals (e.g., cadmium and lead), and some volatile organic compounds (including acrylonitrile). Exclusive e-cigarette users showed 10% to 98% significantly lower concentrations of biomarkers of exposure, including TSNAs, PAHs, most Volatile Organic Compounds, and nicotine, compared with exclusive cigarette smokers; concentrations were comparable for metals and 3 Volatile Organic Compounds. Exclusive cigarette users showed 10% to 36% lower concentrations of several biomarkers than dual users. Frequency of cigarette use among dual users was positively correlated with nicotine and toxicant exposure. Exclusive use of e-cigarettes appears to result in measurable exposure to known tobacco-related toxicants, generally at lower levels than cigarette smoking. Toxicant exposure is greatest among dual users, and frequency of combustible cigarette use is positively correlated with tobacco toxicant concentration. The authors concluded that the findings provide evidence that using combustible tobacco cigarettes alone or in combination with e-cigarettes is associated with higher concentrations of potentially harmful tobacco constituents in comparison with compared to e-cigarettes alone.[268] Device and products: Not reported
Prokopowicz et al.[269] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between **e-cigarettes and levels of cadmium and lead**. Age: 19 and 39 years. Sex: 77 men and 79 women. Country: Poland. Data source: Volunteers. Population size: 156. Data collection period: Not reported E-cigarette, smoking and other related status: four groups: smokers who smoked cigarettes for at least 2 years, dual users who smoked conventional tobacco cigarettes for at least 2 years and used e-cigarette for at least 6 months, e-cigarette users who used e-cigarette for at least 6 months and were former smokers with minimum duration of smoking cessation of 6

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		months and who directly switched from combustible cigarettes to e-cigarette after smoking for at least 2 years, and never-smokers. Non-smokers (n = 51), e-cigarette users (n = 48), Dual e-cigarette users-cigarette smokers (n = 29) and Cigarette-only smokers (n = 28). Outcomes: concentration of Cadmium and Lead in Nicotine Liquids and Electronic Cigarette Aerosols/Smoke. Tank system/cigarette: CE4(1), Pb (mg/L) 0.22–29.26 CE5(2), CE4(3), CE5(4), 3R4f Participants from the e-cigarette group used 12 different brands of second-generation (44 individuals) and third-generation (four individuals) e-cigarettes. The nicotine concentrations of e-liquid used were as follows: 0.1%–0.4% (two individuals); 0.6%–0.9% (15 individuals); 1.0%–1.5% (14 individuals); 1.6%–2.4% (15 individuals); and greater than 2.4% (two individuals). Among the six groups of flavourings, most of the individuals used fruit taste (21 individuals) followed by tobacco taste (11 individuals), menthol taste (eight individuals), and tea/coffee taste (six individuals). Participants from the dual-user group used eight different brands of second-generation (26 individuals) and third-generation (three individuals) e-cigarettes. The nicotine concentrations of e-liquid used were as follows: 0.1%–0.4% (two individuals); 0.6%–0.9% (13 individuals); 1.0%–1.5% (15 individuals); 1.6%–2.4% (15 individuals); and greater than 2.4% (one individual). Among the seven groups of flavourings, most of the individuals used fruit taste (11 individuals) followed by tobacco taste (seven individuals) and menthol taste (seven individuals). The authors concluded that smokers who completely switched to e-cigarettes and quit smoking conventional combustible tobacco cigarettes may significantly reduce their exposure to cadmium, and probably to lead.[269] Device and products: The second-generation Ego-3 battery (3.4 V with voltage stabilization) was used most popularly among the participants in this study. The authors examined four tank systems (two CE4 systems with a top atomizer and two CE5 systems with a bottom atomizer) and convenience samples of 18 e-liquids. Each e-cigarette tank was filled, rotated a few times to ensure the homogeneous distribution of the contents, and stored for at least 24 hours in the dark at room temperature at a horizontal position before the experiment. Each was used for a single brand of e-liquid. The batteries were fully charged before the experiment and were replaced after the charge level reached half of the maximum value, which was signalled by the red diode on the battery. Participants from the dual-user group used eight different brands of second-generation (26 individuals) and third-generation (three individuals) e-cigarettes. The nicotine concentrations of e-liquid used were as follows: 0.1%–0.4% (two individuals); 0.6%–0.9% (13 individuals); 1.0%–1.5% (15 individuals); 1.6%–2.4% (15 individuals); and greater than 2.4% (one individual). Among the seven groups of flavourings, most of the individuals used fruit taste (11 individuals) followed by tobacco taste (seven individuals) and menthol taste (seven individuals).
Rubinstein et al.[271] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on a **range of chemical toxicants** (metabolites of benzene, ethylene oxide, acrylonitrile, acrolein, propylene oxide, acrylamide, and crotonaldehyde) in two groups, **e-cigarette**-only users and never-using controls. Age: 13–18 years. Sex: 68 males 35 females Country: USA. Ethnicity: E-Cigarette–Only Users: Non-Hispanic white 36/67 (54%) Asian American or Pacific Islander 12/67 (19%) Multiracial 10/67 (15%) Hispanic 7/67 (10%) Dual Users: Non-Hispanic white 9/16 (67%) Asian American or Pacific Islander 2/16 (12%) Multiracial 3/16 (19%) Hispanic 2/16 (12%)

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		Controls: Non-Hispanic white 0 Asian American or Pacific Islander 2/20 (10%) Multiracial 0 Hispanic 18/20 (90%) Data source: recruited from the San Francisco Bay area by using fliers and online advertising. Population size: 103 E-Cigarette–Only users n=67 Dual Users n=16 Controls n = 20. Data collection period: Not reported E-cigarette, smoking and other related status: e-cigarette-only users (i.e. >=1 use within the past 30 days, >=10 lifetime e-cigarette use episodes) specifically n= 67 e-cigarette-only users (no cigarettes in the past 30 days) and n = 16 (use of cigarettes in the past 30 days in addition to e-cigarettes); along with N = 20 never-using control Outcomes: Biomarkers of Nicotine, Tobacco-Specific Nitrosamine, and Volatile Organic Toxicants. Biomarkers of Nicotine Saliva cotinine, Urine NNAL (metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific nitrosamine that is a potent carcinogen). Volatile Organic Toxicants metabolites of benzene (PMA), ethylene oxide (HEMA), acrylonitrile (CNEMA), acrolein (3-HPMA), and acrylamide (AAMA) Two groups of e-cigarette-only users specifically n= 67 e-cigarette-only users (no cigarettes in the past 30 days) and n = 16 (use of cigarettes in the past 30 days in addition to e-cigarettes), along with N = 20 never-using controls were assessed. Metabolites of benzene, ethylene oxide, acrylonitrile, acrolein, and acrylamide was significantly higher in dual users versus e-cigarette-only users (all P < .05). Excretion of metabolites of acrylonitrile, acrolein, propylene oxide, acrylamide, and crotonaldehyde were significantly higher in e-cigarette-only users compared with controls (all P < .05). The authors concluded that although e-cigarette vapour may be less hazardous than tobacco smoke, their findings challenged the idea that e-cigarette vapour is safe, because many of the volatile organic compounds identified are carcinogenic[271] Device and products: The following characteristics were reported: Usual type of device - Vape pen, Modified, Juul, Other or unsure; E-cigarettes contain – nicotine (Always, Sometimes, Unsure, Never); Usual flavour of e-cigarette (Fruit, Candy, Menthol Tobacco)
Wei et al.[273] 2018	Harm	The authors reported on the relationship between **e-cigarette** users and **metabolite levels of flame retardants** (and their urinary metabolites. Age: Age (year), Non-user 20–45 years N = 511 >46 years N = 690, Cigarette User 20–45 years N = 142 >46 years N = 156, Cigar User 20–45 years N = 12 >46 years N = 10, E-Cigarette User 20–45 years N = 10 >46 years N = 4 , User of Smokeless Tobacco Products 20–45 years N = 6 >46 years N = 9. Sex: Non-user male = 534, female 667; Cigarette User male = 170, female 128; Cigar User male = 18, female 4; E-Cigarette User male = 8, female 6; User of Smokeless Tobacco Products male = 15, female=0 Country: USA. Data source: National Health and Nutrition Examination Surveys Population size: 1,550. Data collection period: 2013-2014. E-cigarette, smoking and other related status: Exclusive e-cigarette users, exclusive cigarette smokers, exclusive cigar smokers, and exclusive users of smokeless tobacco products were identified if they self-reported use of e-cigarettes, cigarettes, cigar, and smokeless tobacco products, respectively,

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		within the five days prior to examination but never used any other tobacco products Non-user N = 1201, Cigarette User N = 298, Cigar User N = 22 E-Cigarette User N = 14 User of Smokeless Tobacco Products N = 15 Outcomes: Flame retardants and their (urinary metabolites): Triphenyl phosphate (TPhP), (Diphenyl phosphate (DPhP)); Tris(1,3-dichloro-2-propyl) phosphate (TDCPP) (Bis(1,3-dichloro-2-propyl) phosphate (BDCPP); Tris(1-chloro-2-propyl) phosphate (TCPP) (Bis(1-chloro-2-propyl) phosphate (BCPP)); Tris(2-chloroethyl) phosphate (TCEP) (Bis(2-chloroethyl) phosphate (BCEP)); Tri-p-cresyl phosphate (TpCP) (Di-p-cresyl phosphate (DpCP)); Tri-o-cresyl phosphate (ToCP) (Di-o-cresyl phosphate (DoCP)); Tributyl phosphate (TBUP) (Dibutyl phosphate (DBUP)); Tribenzyl phosphate (TBzP) (Dibenzyl phosphate (DBzP)); 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) (2,3,4,5-tetrabromobenzoic acid (TBBA)). Four metabolites had detection rates >60%, the authors observed higher adjusted geometric mean for (bis(2-chloroethyl) phosphate (BCEP)), a metabolite of tris(1-chloro-2-propyl) phosphate (bis(1-chloro-2-propyl) phosphate), tris(2-chloroethyl) phosphate (TCEP), in the users of e-cigarettes than in both non-users and cigarette users, suggesting that using e-cigarettes could lead to elevated exposure to TCEP. In a similar fashion, cigar users may have a higher exposure to triphenyl phosphate (TPhP) while smokeless tobacco (including e-cigarette) users showed higher exposure to tributyl phosphate (TBUP), but lower exposure to triphenyl phosphate. The authors concluded that while the results are preliminary, they indicate a need for a better examination of the types and levels of organophosphate flame retardants and their potential contamination sources in non-cigarette tobacco products, including e-cigarettes.[273] Device and products: Not reported
Jain.[270] 2019	Harm	The authors reported on **concentrations of cadmium, lead, and mercury in blood** among cigarette, cigar, **e-cigarette**, and dual cigarette and e-cigarette users in the USA. Age mean (SD) years: 12 years of age or older. Sex: Not reported Country: USA. Data source: National Health and Nutrition Examination Survey Population size: 1,139 smokers. Data collection period: 2013 to 2016 E-cigarette, smoking and other related status: Smokers were categorized as smokers of cigarettes only, cigars only, cigars and cigarettes, e-cigarettes only, and those who used both cigarettes and e-cigarettes. All other smokers were excluded from the database. Outcomes: concentrations of metals in blood: cadmium, lead and mercury The authors concluded that the observed levels of blood cadmium, lead, and mercury among adults in the USA aged **12 years or over** were not found to differ among cigarette-only users, e-cigarette-only users, and dual users of both cigarettes and e- cigarettes.[270] Device and products: Not reported
Wang et al.[274] 2019	Harm	The authors reported on the relationship between **smoking behaviours in adults and environmental pollutants of polycyclic aromatic hydrocarbons**. Age: Recruitment employed address-based, area-probability sampling, using an in-person household screener to select youth (ages 12–17) and adults. Adult tobacco users, young adults ages 18 to 24, and were oversampled

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers toxicology of e-cigarette constituents
		relative to population proportions. Specifically, 18–24 years, 25–34 years, 35–54 years, and 55 years and older. Sex: Not specifically reported. Country: USA. Ethnicity: African Americans Data source: Population Assessment of Tobacco and Health study Population size: 8,327/11,519. Data collection period: 2013-2014 E-cigarette, smoking and other related status: Participants smoking-related behaviours were grouped as follows: participants based on their use of tobacco products as never-tobacco user (never user, n=1700), exclusive current established combustible products user (combustible products user, n=5767), and exclusive current established non-combustible products user (non-combustible products user, n=860). Tobacco users were further classified as exclusive cigarette user (cigarette user, n=3964), exclusive smokeless product user (SLT user, n=509), and exclusive e-cigarette user (e-cigarette user, n=280). In addition, categorization on the frequency of product use (everyday vs some days) and time since use (last hour, within 3 days, over 3days) was also assessed. Outcomes: Seven urinary OH-PAH metabolites: biomarkers, 1-Hydroxynaphthalene, 2-Hydroxynaphthalene, 2-Hydroxyfluorene, 3-Hydroxyfluorene, 1-Hydroxyphenanthrene, Σ2,3-Hydroxyphenanthrene and 1-Hydroxypyrene Geometric mean (GM) concentrations and evaluated associations between tobacco product user categories and **polycyclic aromatic hydrocarbon** biomarker concentrations were reported. For all biomarkers examined, cigarette users had the highest geometric means compared to other tobacco product users. Interestingly, geometric means of 2-hydroxyfluorene, 3-hydroxyfluorene, and 2,3-hydroxyphenanthrene were significantly higher in exclusive smokeless product users than in e-cigarette users; 3-hydroxyfluorene and 1-hydroxypyrene were also significantly higher in e-cigarette and exclusive smokeless product users than in never users. Everyday cigarette and exclusive smokeless product users had significantly higher geometric means for most biomarkers than sometimes users; cigarette and exclusive smokeless product users who had used the product in the last hour had significantly higher geometric means of most biomarkers than other occasional cigarette or exclusive smokeless product users. By contrast, everyday e-cigarette users' geometric means of most biomarkers did not differ significantly from those in sometimes e-cigarette users.[274] Device and products: Not reported

Table 73: Cross-sectional surveys papers on other outcomes, benefits or harms

Author(s) year	Possible benefit or harm	Cross-sectional surveys papers other outcomes
Ballbè et al.[278] 2014	Harm	The authors reported on the relationship between **passive exposure** to **nicotine** in conventional combustible tobacco cigarettes and **e-cigarettes** in 54 non-smoker volunteers from different homes. Age: Not reported. Sex: Not reported. Country: Spain Data source: convenience sample. Population size: 54 Data collection period: November 2011 and February 2012 E-cigarette, smoking and other related status: 54 non-smoker volunteers from different homes: 25 living at home with conventional smokers, 5 living

		with nicotine e-cigarette users, and 24 from control homes (not using conventional tobacco cigarettes neither e-cigarettes). The study group of 25 persons lived at home with conventional smokers, of 5 persons lived with nicotine e-cigarette users, and 24 persons were from a control homes (not using conventional tobacco cigarettes neither e-cigarettes). Outcomes: airborne nicotine at home and biomarkers (cotinine in saliva and urine). Salivary and urinary cotinine were highly correlated (Spearman's rank correlation coefficient (rsp)=0.855, p>0.01) and both biomarkers were highly correlated with air nicotine concentration measured at the volunteers' home for one week (rsp=0.731for salivary cotinine and rsp=0.710 for urinary cotinine p-values p<0.001). The authors concluded that non-smokers passively exposed to e-cigarettes absorb nicotine.[278] Device and products: Thee-cigarette devices (all tank system) and the e-cigarette liquid brands (propylene glycol-based liquids) were of different brands (Totally Wickeds, Puffs, and FreeLifes).
Chen *et al.*[283] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on how symptoms that adolescents experience during their first time using a cigarette predict their current use, but little is known about the **symptoms experienced during first e-cigarette use**. Age: 13 to 17 years. Sex: Male 54 Female 57 Transgender 1. Country USA Data source: adolescents between ages 13–17 residing in North Carolina or California with a parent or guardian who participated in a randomized trial of pictorial cigarette pack warnings. The parents or guardians who participated in the randomized trial were recruited through advertisements posted on social media and in retail outlets, buses, and local newspapers. Population size: 112 participants, 41 of which had tried a cigarette or electronic cigarette Data collection period: December 2014 and September 2016 E-cigarette, smoking and other related status: 12 had tried cigarettes only, 12 had tried e-cigarettes, and 17 had tried both. Sixteen percent of adolescents who tried e-cigarettes only and 33% of adolescents who tried cigarettes only report smoking/vaping in the last 30 days. Among the 17 participants who tried both cigarettes and e-cigarettes, 76% reported being a current user: 3 currently smoked cigarettes, 3 currently used e-cigarettes only, and 7 continued to use both. Outcomes: symptoms that adolescents experienced during their first-time using cigarettes and e-cigarettes. The symptoms were coded as negative (felt bad, coughing/chest pain, bad taste in mouth, upset stomach, and dizzy/lightheaded, with a range from 0 to 5) and positive (rush/buzz, and felt relaxed, with a range from 0 to 2) symptoms from their first cigarette and e-cigarette use. Of the 29 adolescents who had tried conventional combustible tobacco cigarettes, 28 had reported results, 22 (76%) reported experiencing negative symptoms only, 2 (7%) reported feeling neutral only, and 4 (14%) reported experiencing both positive and negative symptoms. No participants reported positive symptoms only. The negative symptoms that adolescents reported included feeling dizzy, sick, bad taste in their mouth, difficulty breathing, and headache. By contrast, of the 29 adolescents who had tried e-cigarettes, 9 (31%) reported experiencing negative symptoms only, 12 (41%) reported feeling neutral only, 6 (21%) reported experiencing positive symptoms only, and 2 (7%) reported experiencing both positive and negative symptoms. Twenty-five of the 29 adolescents (86%) reported that they felt 'normal', 'no change', or 'the same' after their first e-cigarette. Adolescents reported fewer negative symptoms from their first e-cigarette

		than from their first cigarette, and e-cigarette symptoms did not influence use as they do for cigarettes.[283] Device and product: Not reported
Mantey *et al*.[282] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between cigarette**, e-cigarette**, hookah, and cigar products and **symptoms at first use** (nausea, coughing, relaxation, rush/buzz, and dizziness). Age of Initiation years mean (sd) E-Cigarettes 13.78 (1.43), Cigarettes 12.35 (2.41) Hookah 13.69 (1.77) Large Cigar/Cigarillo/LFCs 12.97 (2.16). 6th, 8th and 10th grade students in four metropolitan areas of Texas (n=3,907/N=461,069) Sex: 49% female. Country: Four metropolitan areas, Texas USA. Data source: Texas Adolescent Tobacco and Marketing Surveillance System Population size: n=3,907/N=461,069 Data collection period: October 2014 to June 2015 E-cigarette, smoking and other related status: Subjective experiences of first use were assessed among ever users of any nicotine product. Ever use was assessed by the question "Have you EVER tried [product], even once? Remember, marijuana DOES NOT count." with those responding "yes" defined as "ever users." Participants who reported ever use of cigarettes, e-cigarettes, hookah, large cigars, or little filtered cigars (LFC) or cigarillos, were asked if they experienced five different subjective experiences at first use. Outcomes: Nausea, coughing, relaxation, rush/buzz, and dizziness at first use were assessed for cigarettes, e-cigarettes, hookah, and cigar product The authors concluded that subjective experiences at first use differ by tobacco product.[282] Device and products: Not reported
Yao *et al.*[280] 2017	Harm	The authors examined the relationship between **spending on e-cigarettes**, **30-day e-cigarette use,** and **disease symptoms** among current adult cigarette smokers. Age: 2 to 44 years n= 199, 45 to 64 years n= 295, >=65 years n=39 Sex: 217 males, 316 females. Country: USA Ethnicity: Non-Hispanic African American n=35 Non-Hispanic Asian n=9 Non-Hispanic Others n=15 Non-Hispanic White n=429 Hispanic n=45 Data source: Tobacco and Attitudes Beliefs Survey Population size: 539. Of whom, 262 of them were current (last 30 days) e-cigarette users. After excluding 6 participants with missing information on CPD (N = 3, 0.6%) or race/ethnicity (N = 3, 0.6%), the final study sample consisted of 533 participants. Data collection period: August 2015 E-cigarette, smoking and other related status: current cigarette smokers and e-cigarette ever users current (last 30 days) e-cigarette use. Current e-cigarette use was measured by a dichotomous (yes/no) variable based on the answer to the question: Have you used e-cigarettes in the last 30 days? Outcomes: Fifteen disease symptoms were examined: coughing, wheezing, shortness of breath, chest tightness, headache, sore throat, waking up feeling tired, chest pain, having trouble falling asleep or staying asleep, toothache, sensitive teeth, noticing blood when brushing their teeth, having sores or ulcers in their mouth, having one cold, and having more than one cold.

		The authors reported that those who spent money on e-cigarettes were more likely to report chest pain (AOR: 1.25; 95% CI: 1.02–1.52), to notice blood when brushing their teeth (AOR: 1.23; 95% CI: 1.02–1.49), to have sores or ulcers in their mouth (AOR: 1.36; 95% CI: 1.08–1.72), and to have more than one cold (AOR: 1.36; 95% CI: 1.05–1.78) than those with no spending on e-cigarettes in the past 30 days in an adjusted analysis. After controlling for cigarettes smoked per day and other covariates, there were no significant relationships between 30-day e-cigarette use and symptoms.[280] Device and products: Not reported
Choi *et al.*[275] 2018	Possible harm	The authors reported on the relationship between **smoking behaviour patterns and glycated haemoglobin levels**. Age: 20 to >=70 years Sex: Men and women comprised 39.99% (n = 3523) and 60.01% (n = 5286) of the sample, respectively. Country: South Korea Data source: Korea National Health and Nutrition Examination Survey (KNHANES) Population size: 8,809 of 23,080 participants in the nationwide survey database study were assessed in the study Data collection period: 2014-2016 E-cigarette, smoking and other related status: Regarding smoking behaviours, dual smokers, single smokers, ex-smokers, and non-smokers accounted for 1.61% (n = 142), 15.43% (n = 1359), 18.78% (n = 1654), and 64.18% (n = 5654) of the sample, respectively Outcomes: and glycated haemoglobin (HbA1c) levels In the study, persons with a diabetes related diagnosis or missing data (smoking behaviour, HbA1c level, age, sex, occupation, household income, educational level, physical activity, body mass index (BMI), alcoholic behaviour, pack-years of smoking, anaemia status, family history of diabetes mellitus, and caloric intake) were excluded. Participant were classified into four categories: dual smokers (both cigarettes and e-cigarette), single smokers (cigarettes smokers), former smokers (ex-smokers), and non-smokers. Normal weight/underweight, overweight, and obese subjects comprised 46.48% (n = 4094), 22.90% (n = 2017), and 30.63% (n = 2698) of the sample, respectively. The overall mean HbA1c level was 5.48 +/- 0.27%. In the reported findings, elevated **glycated haemoglobin levels** (HbA1c) levels were observed among subjects who were dual users of e-cigarettes and conventional combustible tobacco cigarettes and who were e-cigarette-only or conventional combustible tobacco cigarette-only users, compared with those among non-smokers; however, a direct association between e-cigarette use and HbA1c levels was not reported. In the analyses stratified by sex, men who were dual users and e-cigarette only or conventional combustible tobacco cigarette-only users had higher HbA1c levels than non-smokers, whereas among women, there were no significant results. Among physically inactive subjects, dual users were more strongly associated with elevated HbA1c levels. However, it remains unclear whether e-cigarette use alone can induce an increase in HbA1c levels. According to body mass index, dual users had a strong association of elevated HbA1c levels among people who were obese and overweight compared with those who were average weight and underweight.[275] Device and products: The authors reported a limit to the study was they were not able to consider the type of e-cigarette, frequency of vaping, or concentration of nicotine. That data regarding smoking behaviour, health

		behaviour, and socioeconomic status were collected via self-report surveys and thus might have been subject to recall bias and underestimated smoking behaviours. Finally, they could not consider each single e-cigarette smoking behaviour because the number of single e-cigarette smokers was very small. It should be noted that the relationship of e-cigarette alone with the outcome not examined.
Kyriakos[284] 2018	Harm	The author reported on the characteristics and correlates of **e-cigarette product attributes and undesirable events** during use. Age: 15 to 55+ years. Sex: Reported numbers were for a larger population group than those reported on in this paper Country: Germany, Greece, Hungary, Poland, Romania, Spain Data source: cross-sectional survey with a nationally representative sample of adult cigarette smokers Population size: 6,011, 1,178 reported ever use of e-cigarette (at least once in their life-time) Data collection period: June to September 2016 E-cigarette, smoking and other related status: adult cigarette smokers reporting e-cigarette use Outcomes: characteristics and correlates associated with e-cigarette product attributes and identified correlates of experiencing undesirable events during e-cigarette use The author reported that current daily or weekly prevalence of e-cigarette use among a sample of adult smokers was 7.5%. The most common attributes of e-cigarettes used included those that are flavoured, contain nicotine, and are of tank style. Use of e-liquid refill nozzle caps, described as easy for a child to open, was associated with spilling during refill. Participants who occasionally or regularly adjusted the power (voltage) or temperature of their e-cigarette had greater odds of ever experiencing a 'dry puff'. Mixing different e-liquids was associated with leaking during use and spilling during refill. The author concluded that ongoing evaluation of factors associated with e-cigarette attributes, and of the correlates of experiencing undesirable events during e-cigarette use to product design, is crucial to monitoring the impact of the implementing Acts of the EU Tobacco Products Directive.[284] Device and products: The types of devices and products were not specifically reported but data using the following question was collected. What type of e-cigarettes is your usual/current brand? It is disposable, not refillable (non-rechargeable). It uses replaceable pre-filled cartridges (rechargeable). It has a tank that you fill with liquids (rechargeable). What flavours of e-cigarette or e-liquid have you used in the last 30 days? What is the nicotine strength (mg/mL) of current/last e-liquid? Do you ever mixed e-liquids? Does the e-cigarette or vaping device you use most frequently contain settings to adjust the power (voltage) or temperature?
Abafalvi et al.[281] 2019	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between **e-cigarette**-only users and dual e-cigarette and conventional combustible tobacco cigarette users with a range of 16 **adverse events** and 10 **physiological functions**. Age: 18 to 75 years. Sex: 859 males 177 females. Country: Hungary. Data source: Convenience sample. Population size: 1042 Data collection period: September–December 2015 E-cigarette, smoking and other related status: E-cigarette-only user n=859, Dual users n=183. E-cigarette-only versus dual use was assessed by a question "Do you use e-cigarette or combustible cigarette?" (combustible cigarettes only, e-cigarettes only, both of them). Only persons who were e-cigarette-only users and dual users were included in the study. Past

		combustible cigarette use was measured by the number of tobacco cigarettes smoked per day before initiating e-cigarette use. Response options were categorized into: ≤10 CPD – light smoker, 11–19 CPD – moderate smoker, ≥20 CPD – heavy smoker. Current e-cigarette use characteristics variables included in this study were (1) time since respondent started using e-cigarettes (< 6 month ago, 6–12 months ago, 1–2 years ago, > 2 years ago), (2) frequency of e-cigarette use per day (non-daily, 1–10 times a day, 11–19 times a day, ≥20 times a day), and (3) nicotine concentration of the e-liquid (0 mg/ml – 18 mg/ml or more) Outcomes: adverse events: sore/dry mouth and throat, cough, mouth or tongue sores/inflammation, gingivitis, gum bleeding, headache, dizziness, heart palpitation, breathing difficulties, chest pain, sleepiness, sleeplessness, allergy, black tongue, nose bleeding, any adverse event physiological functions: breathing, smell, taste, physical status in general, stamina, mood, quality of sleep, appetite, sexual performance and memory The convenience sample was obtained by posting the survey on Hungarian e-cigarette forum websites and an e-cigarette web shop inviting website visitors to participate. Participants reported the occurrence of adverse events and changes in physiological functions since they switched from smoking to e-cigarette use or while dually using e-cigarettes and combustible cigarettes. Confirmatory factor analysis with covariates was applied to explain perceived health changes due to e-cigarette-only use and dual use. Of the 1,584 initial respondents 1,042 unique respondents who ever smoked and were current e-cigarette users (only or dual users) were included in the study. The authors concluded that the dual users were significantly more likely to report adverse events of vaping than e-cigarette-only users (26.2% versus 11.8%; p<0.001). Experiencing health improvements was significantly more likely among e-cigarette-only users than among dual users for all surveyed physiological functions. E-cigarette-only users reported larger effects of vaping on sensory, physical functioning, and mental health factors compared with dual users[281] Device and product: Information on 'Frequency of e-cigarette use', 'Combustible cigarettes smoked per day (before started using e-cigarette', and 'Nicotine concentration of e-liquid' was gathered and reported. No specific information on the devices used was reported.
Atuegwu *et al.*[276] 2019a	Harm	The authors reported on the association of **e-cigarette** use with a self-reported **diagnosis of prediabetes** in never cigarette smokers. Age mean (SD) years: 18 to 55 years. Sex: 56% males, 44% females Country: USA. Ethnicity:White only, Non-Hispanic, Black only, Non-Hispanic, Other race or multiracial, Non-Hispanic and Hispanic Data source: Behavioral Risk Factor Surveillance System Population size: 154,404. Data collection period: 2017 E-cigarette, smoking and other related status: 143,952 never, 1,339 current and 7,625 former e-cigarette users Outcomes: diagnosis of prediabetes. Current e-cigarette users had an increased odds of reporting a diagnosis of prediabetes 1.97 (95% CI 1.25–3.10) compared to never e-cigarette users. After stratifying by gender, men and women had an increased odds ratio of reporting a diagnosis of prediabetes 2.36 (95% CI 1.26–4.40) and 1.88 (95% CI 1.00–3.53) respectively when compared to never e-cigarette users. There was no association between former e-cigarette use and a self-reported diagnosis of prediabetes.

		The authors concluded that e-cigarette use may be associated with self-reported prediabetes[276] Device and products: Not reported
Chang *et al.*[285] 2019	Harm	The authors reported on the relationship between **e-cigarette use** and **self-reported health outcomes.** Age: 18 to 75 years plus, the majority, 5844, were under 35 years of age Sex: 5182 males 4870 females. Country: USA Ethnicity: 7771 while, 1177 black alone, 1104 other Data source: Population Assessment of Tobacco data Population size: 10,052 - 6,311 current smokers and 3,741 non-smokers Data collection period: 2013-2014 E-cigarette, smoking and other related status: six variables were selected to describe subject's patterns of e-cigarette use - own an e-cigarette. number of e-cigarette cartridges used in entire life, ever smoked e-cigarettes fairly regularly, used flavoured e-cigarettes, e-cigarettes used usually contain nicotine and concentration of nicotine in e-cigarette cartridge Outcomes: Four self-reported categorical variables to assess respondents' health conditions including overall health, mental health, physical health, and quality of life. The categories include self-rated measurements on each variable: excellent, very good, good, fair, and poor. Chang et al reported-on findings from a nationally representative sample. They reported measures of physical and mental health and quality of life using relative risk ratio (RRR) and 95% confidence interval (95% CI) for self-reported health outcomes between reference and comparison groups, estimated by multinomial logistic regression in non-smoking population (n = 3,741); stratified by the categories of: Own an e-cigarette, Number of cartridges used in entire life, Ever smoked e-cigarettes fairly regularly, Used flavoured e-cigarettes and E-cigarettes used usually contain nicotine and Concentration of nicotine in e-cigarette cartridges. The reported statistical assessment, of relative risk ratio (RRR) found non-cigarette smoker who used e-cigarettes had lower levels of mental health in comparison to non-smoking non e-cigarette users – RRR 0.66. When the respondents used e-cigarette products containing nicotine, the risk for reporting poor mental health was higher (RRR = 1.87). Among cigarette smokers, more use of e-cigarette cartridges was associated with higher risk of mental health (RRR = 1.12). Poor quality of life was associated with regular e-cigarette use. If smokers used e-cigarette products with nicotine, the risk of reporting poor quality of life was lower than individuals who did not use such products (RRR = 0.49). Higher concentration of nicotine in e-cigarette cartridges was associated with higher risks of poor physical and poor overall health, and with lower chance of excellent mental health. The authors concluded that some e-cigarette usage patterns were associated with poorer health conditions in smoking and non-smoking populations, but that they were cautious about making conclusive claims regarding e-cigarette usage patterns.[285] Device and products: The authors stated among respondents the questions on "E-cigarettes used usually contain nicotine" and "Concentration of nicotine in e-cigarette cartridge" had many skipped responses, they therefore classified those inapplicable responses to "unknown" or "I don't know the concentration."
Md Isa *et al.*[277] 2019	Harm	The authors reported on the **tear function** in **e-cigarette** vapers. Age mean (SD) years: Not reported. Sex: All males. Country: Malaysia

		Data source: cross-sectional, single-visit, pilot study carried out at the National Institute of Ophthalmic Sciences Optometry Clinic Population size: 42. Data collection period: 2017 E-cigarette, smoking and other related status: 21 vapers and 21 healthy non-smokers Outcomes: dry eye and tear film quality The authors concluded that vapers showed moderate to severe symptomatic dry eye and poorer tear film quality compared with non-smokers. High vaping voltage may have aggravated the dry eye syndrome because of hazardous by-products from pyrolysis of the e-liquid constituents.[277] Device and products: Not reported
Northrup *et al*.[279] 2019	Harm	The authors reported on the contribution of medical staff to **third-hand smoke contamination in a neonatal intensive care unit.** Age mean (SD) years: 36.0 (10.4). Sex: 215 females. Country: USA Data source: medical staff recruited from a large, urban children's hospital in Houston, Texas with a 144-bed neonatal intensive care unit and over 1000 admissions per year. Population size: 246. Data collection period: 2017 E-cigarette, smoking and other related status: The authors explored contamination routes by characterizing nicotine levels (THS proxy) found on the fingers of neonatal intensive care units medical staff and assessed finger-nicotine correlates Outcomes: measurable finger nicotine The authors concluded that almost four in five neonatal intensive care unit medical staff had measurable finger nicotine, with finger surface area and frequency of reported exposure to tobacco smoke in friends' or family members' homes emerging as important correlates, leading to third-hand nicotine contamination in a neonatal intensive care unit.[279] Device and products: Not reported

Appendix 4: Longitudinal cohort study papers by adapted Academies of Sciences framework headings for e-cigarettes

Table 74: Longitudinal cohort study papers on dependency and abuse liability, benefits or harms

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
Caponnetto *et al.*[292] 2013	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship **of e-cigarette use with smoking reduction and smoking cessation**. Age: 44.6 (±12.5) years), Sex: 6 male, 8 females. Country: Italy Data source: Chronic schizophrenic in-patients, who smoked ≥20 factory-made cigarettes per day (cig/day) for at least the past 10 years, able to understand the assessment procedures, and to provide written informed consent were recruited from the "C.T.A, Villa Chiara-Psichiatrica Riabilitativa e Ricerca", Mascalucia (in Catania). Population size: 14 Data collection period: Year not reported. Study participants were invited to attend six study visits: at baseline, week-4, week-8, week-12 week-24 and week 52. The follow up period was 52-weeks. E-cigarette, smoking and other related status: Pack Years mean (SD) 28.8 (±12.9). Level of nicotine dependence by using Fagerstrom Test of Nicotine Dependence Outcomes: The primary efficacy measure was sustained 50% reduction in the number of cigarettes/day at week-52 from baseline (reducers); defined as sustained self-reported 50% reduction in the number of cigarette/day compared to baseline for the 30 days period prior to week-52 study visit. Carbon monoxide levels in exhaled breath were measured to objectively verify smoking status and to document a reduction compared to baseline). An additional secondary efficacy measure of the study was sustained smoking abstinence at week-52 (quitters); defined as complete self-reported abstinence from tobacco smoking (not even a puff) for the 30 days period prior to week-52 study visit carbon monoxide levels in exhaled breath levels were measured to objectively verify smoking status with an carbon monoxide levels in exhaled breath concentration of ≤10 ppm). Those smokers who failed to meet the above criteria at the final week-52 follow-up visit (study visit 6) were categorized as reduction/cessation failures (failures). Sustained 50% reduction in the number of cigarettes/day at week-52 was shown in 7/14 (50%) participants; their median of 30 cigarettes/day decreasing significantly to 15 cigarettes/day (p = 0.018). Sustained smoking abstinence at week-52 was observed in 2/14 (14.3%) participants. Combined sustained 50% reduction and smoking abstinence was shown in 9/14 (64.3%) participants. Nausea was observed in 2/14 (14.4%) of participants, throat irritation in 2/14 (14.4%) of participants, headache in 2/14 (14.4%) of participants, and dry cough in 4/14 (28.6%) of participants. However, these adverse events diminished substantially by week-24. The authors concluded that e-cigarette use substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients who smoked and did not intend to quit. This was achieved without negative impacts on the symptoms of schizophrenia as assessed by the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms.[292] Device and products: an e-cigarette ("Categoria" e-Cigarette, Arbi Group Srl, Milano, Italy). A full 4-weeks supply of 7.4 mg nicotine cartridges ("Original" cartridges, Arbi Group Srl, Milano, Italy) was also provided and participants were trained on how to load them onto the e-cigarette's atomizer. Random

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		checks confirmed that the nicotine content per cartridge was 7.25 mg. Detailed toxicology and nicotine content analyses of "Original" cartridges had been carried in a laboratory certified by the Italian Institute of Health.
Bandiera *et al.*[294] 2017	Harm	The authors reported on the relationship between **depressive symptoms and current e-cigarette use**. Age: 18 to 29-year-old. Sex: ~64% female. Country USA. Ethnicity: Hispanic, Asian, White, Bi-ethnic or Bi-racial, African-American, Native-American/Pacific-Islander, other Data source: Participants were recruited from 24 colleges located in the five counties surrounding Austin, Dallas/Fort Worth, Houston, and San Antonio, Texas. A three-panel cross-lagged panel analysis was used to examine the bidirectional associations between current e-cigarette use and depressive symptoms across three study waves. Cross-lagged associations were assessed with direct paths from e-cigarette use to depression in the subsequent wave (6 months later) and from depression to e-cigarette use in the subsequent wave (6 months later). Four stability paths from each variable to their respective subsequent follow-up outcome variables (e.g., wave 1 depressive symptoms to wave 2 depressive symptoms) were also included. Thus, findings for the cross-lagged paths can be interpreted as being over and above the influence of the stability paths. Population size: 5,482 wave 1, 4,303 wave 2, 4,293 wave 3 Data collection period: Initial assessment was from November 2014–February 2015 and every 6 months thereafter for two subsequent waves (waves 2 and 3). This was a 12-month follow-up study E-cigarette, smoking and other related status: Use of four types of tobacco products at wave 1, besides e-cigarettes, was included as covariates. Current or past 30-day use of cigarettes, smokeless/snus tobacco, large cigars/cigarillos/little cigars, and hookah was assessed. Participants reporting use of a product on one or more days in the past 30 days were given a score of 1 for that product. Scores for the four items were summed to create an index of the number of other tobacco products used in past 30 days (range = 0–4). Current use of e-cigarette use was assessed with the question "During the past 30 days, have you used any ENDS product (i.e., an e-cigarette, vape pen, or e-hookah), even one or two puffs, as intended (i.e., with nicotine cartridges and/or e-liquid/e-juice)?" The item was scored 0 (used on 0 days in the past 30 days) or 1 (used on 1 or more days in the past 30 days). Outcomes: e-cigarette use and depression were predictive of their respective constructs after six months The authors concluded that elevated depressive symptoms predicted e-cigarette use 6 months later among a young adult college population, even after controlling for a variety of sociodemographic characteristics and the number of tobacco products used. However, they found no evidence that e-cigarette use predicted elevated depressive symptoms.[294] Device and products: Not reported
Lechner *et al.*[295] 2017	Harm	The authors reported on the relationship between **baseline depressive symptoms and onset of e-cigarette use, tobacco cigarette use, and dual use** at follow-ups. Age: baseline mean age = 14.1 (SD = 0.41). Sex: 53.4% female

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		Ethnicity: Country USA. 44.1% Hispanic, 19.0% Asian, 16.2%White, 5.6% Bi-ethnic or Bi-racial, 4.8% African-American, 4.1% Native-American/Pacific-Islander, 5.5% other Data source: Data were drawn from a longitudinal study (baseline [wave 1], 6-month follow-up [wave 2], and 12-month follow-up [wave 3]) of substance use and mental health among high school students in the Los Angeles, CA metropolitan area. Population size: data was collected for 3,383 (99.6%), 3,293 (97.0%), and 3,282 (96.6%) participants, at baseline and 6- and 12-month follow-ups, respectively Data collection period: 2013 and 2014. Baseline [wave 1], a 6-month follow-up [wave 2] and 12-month follow-up E-cigarette, smoking and other related status: lifetime and past 6-month use of e-cigarettes (described as "e-cigarettes, personal vaporizers") and combustible cigarettes were measured at each wave (yes/no). Frequency of e-cigarette use, and cigarette use within the last 30 days (scored as a 6-level variable: 0 = 0 days, 1 = 1−2 days, 2 = 3−5 days, 3 = 6−9 days, 4 = 10−14 days, 5 = 30 days) was assessed only at wave 3. Outcomes: Higher baseline depressive symptoms predicted subsequent onset of tobacco cigarette use (OR: 1.024; 95% CI: 1.009−1.055), e-cigarette use (OR: 1.015; 95%CI: 1.003−1.023), and dual use of both products (OR: 1.021; 95%CI: 1.003−1.043). Sustained use of e-cigarettes over the 12-month observation period (versus non-use) was associated with a greater rate of increase in depressive symptoms over time (B=1.272; standard error [SE]=0.513; *P*=0.01). Among those who sustained use of e-cigarettes, higher frequency of use was associated with higher depressive symptoms at the final follow-up (B=1.611; *p*=0.04). The authors concluded that a bi-directional association of depressive symptoms with e-cigarette use onset across mid-adolescence was observed.[295] Device and products: Not reported
Manzoli *et al*.[289] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on findings from a cohort study regarding **e-cigarette use effectiveness and safety** at 24 months. Age: 30 to 75 years. Sex: Not reported. Country Italy Data source: Participants were recruited through direct contact with general practitioners and e-cigarette shops, via internet advertisement and social networks Population size: 1,355 subject provided baseline data: 343 users of e-cigarettes only, 319 users of both cigarettes (dual users), 369 smokers of tobacco cigarettes only Data collection period: recruitment was June to November 2013. The study updated previous 12-month findings and report the results of the 24-month follow-up E-cigarette, smoking and other related status: Participants were classified as tobacco smokers, if they smoked ≥1 tobacco cigarette/day (2) e-cigarette users, if they inhaled ≥50 puffs/week of any type of e-cigarette and (3) dual users, if they smoked tobacco cigarettes and used e-cigarettes Outcomes: Sustained abstinence from tobacco cigarettes and/or e-cigarettes after 24 months, the difference in the number of tobacco cigarettes smoked daily between baseline and 24 months, possibly related serious adverse

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		events. Data at 24 months were available for 229 e-cigarette users, 480 tobacco smokers and 223 dual users (overall response rate 68.8%). Of the e-cigarette users, 61.1% remained abstinent from tobacco (while 23.1% and 26.0% of tobacco-only smokers and dual users achieved tobacco abstinence). The rate (18.8%) of stopping use of either product (tobacco and/or e-cigarettes) was not higher for e-cigarette users compared with tobacco smokers or dual users. Self-rated health and adverse events were similar between all groups. Among those continuing to smoke, there were no differences in the proportion of participants reducing tobacco cigarette consumption by 50% or more, the average daily number of cigarettes and the average self-rated health by baseline group. Most dual users at baseline abandoned e-cigarettes and continued to smoke tobacco. Those who continued dual using or converted from tobacco smoking to dual use during follow-up experienced significant improvements in the 3 outcomes compared with those who continued or switched to only smoking tobacco ($p<0.001$). The authors concluded that e-cigarette use alone might support tobacco quitters in remaining abstinent from smoking. However, dual use did not improve the likelihood of quitting tobacco or e-cigarette use, but may be helpful in reducing tobacco consumption. Adverse event data were scarce and must be considered preliminary.[289] Device and products: Not reported
Russo *et al*.[297] 2018	Benefit	The authors reported on the relationship between **e-cigarette use and post-cessation weight increase**. The authors concluded that there was no evidence of post-cessation weight increase in those who substantially reduced tobacco cigarette consumption by switching to e-cigarettes (i.e. dual users), and only modest post-cessation weight increase was reported in exclusive e-cigarette users at 12-month follow-up. By reducing weight gain and tobacco consumption, e-cigarette-based interventions may promote an overall improvement in quality of life Age: E-cigarette users study group n=86, Cigarette smokers study group n= 93, Quitters study group n= 44 Sex (male/female): E-cigarette users study group 58 males 28 females Cigarette smokers study group 59 males 34 females Quitters study group 29 males 15 females Country: Italy Data source: medical records review of patients with cardiorespiratory conditions regularly followed-up at the outpatient clinics of four Italian hospitals. Baseline and follow-up data were extracted from patients' medical records over a period of approx. 3.5 years Population size: 223 Data collection period: March 2012 to December 2015 E-cigarette, smoking and other related status: Patients reporting regular daily use of e-cigarettes (and if at all conventional tobacco cigarettes) on at least two consecutive follow-up visits (timed at approx. 6 and 12 months) were eligible for inclusion (e-cigarette users study group). Datasets from chart review of a second group of age-, sex-matched patients reporting to be regular smokers (and not using e-cigarettes) over the same observation period from the same participating clinics were selected as reference (cigarette smokers study group). Consecutive follow-up visits were timed as for the e-cigarette's users study group (at approx. 6 and 12 months from baseline). Data from age-, sex-matched smokers in good general health who reported sustained smoking abstinence (for equal or more than 6 months)

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		after successfully completing a cessation program based on licensed medications (nicotine patch, bupropion, or varenicline) in combination with counselling at the local smoking cessation centre was also collected. Baseline and follow-up data were extracted from clinic records of patients regularly followed-up at the smoking cessation centre over a period of approx. 3 years (February 2013 to January 2016). Their baseline measures were obtained before enrolling in the smoking cessation intervention (when they were smoking). For those who achieved documented sustained abstinence, consecutive follow-up visits were timed at approx. 6 and 12 months from baseline. Outcomes: change in body weight from baseline to the final follow-up visit at about 1 year The authors concluded that there was no evidence of post-cessation weight increase in those who substantially reduced tobacco cigarette consumption by switching to e-cigarettes (i.e. dual users), and only modest post-cessation weight increase was reported in exclusive e-cigarette users at 12-month follow-up. By reducing weight gain and tobacco consumption, e-cigarette-based interventions may promote an overall improvement in quality of life.[297] Device and products: The authors reported details of e-cigarette devices and e-liquid nicotine strengths were gathered at the 12-month visit, however information was not recorded in the paper
Du *et al.*[291] 2019	Harm, but less harmful than tobacco cigarettes	The authors reported on changes in **e-cigarette use behaviours and dependence** in long-term e-cigarette users. Age mean (SD) years: Exclusive e-cigarette users at follow-up: Baseline 41.2 (11.9) Follow-up 44.9 (11.9) Poly users (e-cigarette and other tobacco products) at follow-up: Baseline 36.5 (11.9) Follow-up 40.1 (11.9) Sex: Exclusive e-cigarette users at follow-up -baseline - 278 (67.5) males, Follow-up 38 (64.4) males Country: USA Data source: study subjects were recruit through various online sources and were invited to complete an online survey of e-cigarette use. Population size: 494 Data collection period: 2014-2014 with a follow-up online survey in 2017-2018. A mean follow-up time of 3.7 years (SD=0.7; range, 2−6 years) for the analyses E-cigarette, smoking and other related status: The authors reported at baseline, 402 subjects (81.4%) were exclusive e-cigarette users, and 71 subjects (14.4%) were poly users. Among baseline exclusive e-cigarette users, the majority (88.3%) continued using e-cigarettes exclusively, but 37 users (9.2%) became poly users and 1 returned to cigarette smoking at follow-up. Among baseline poly users, 60.6% became exclusive e-cigarette users at follow-up. The mean Penn State Electronic Cigarette Dependence Index score remained similar over time (8.4 at baseline vs 8.3 at follow-up. To evaluate changes in e-cigarette-use behaviours, repeated 7-day point prevalence measures were used to categorize study subjects as exclusive e-cigarette users, poly users, and ex-e-cigarette users at baseline and follow-up. Study subjects were classified into 5 groups according to their past-7-day use of e-cigarettes and other tobacco or nicotine products (including any cigarettes, chewing tobacco, snuff/dipping tobacco, snus, pipe tobacco, or other nicotine products such as patch, gum, lozenge, inhaler, or nasal spray). “Exclusive e-cigarette users” were subjects who had used only e-cigarettes, “poly users with other nicotine products” were subjects who used both e-cigarettes and

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		any other nicotine product, "poly users with other tobacco products" were those who had used both e-cigarettes and any other tobacco product, "ex–e-cigarette users with cigarettes" were subjects who did not use an e-cigarette but consumed cigarettes, and "other ex–e-cigarette users" were subjects who did not use an e-cigarette or any cigarettes. The e-cigarette use behaviour at baseline was compared with the follow-up behaviour to evaluate if an individual's e-cigarette use behaviour persisted or changed over time. Outcomes: changes in e-cigarette use behaviours and e-cigarette–related dependence measured using the Penn State Electronic Cigarette Dependence Index The authors concluded that findings suggest that the risk of relapse to cigarette smoking is low, and that e-cigarette-related dependence remains stable, in long-term e-cigarette users.[291] Device and products: Not reported
Marsden *et al.*[298] 2019	Harm	The authors reported on the association between frequency of **cigarette and alternative tobacco product use and depressive symptoms**. Age mean (SD) years: 21 (2.3). Sex: 1919 males, 3,317 females Country: USA Data source; Texas college students. First six waves of the Marketing and Promotions across Colleges in Texas project (M-PACT). M-PACT is a prospective cohort study of Texas college students. M-PACT began in November 2014 with follow up at six-month intervals through May 2017 Population size: 5,236 Data collection period: 2014 to 2017 E-cigarette, smoking and other related status: Past 30-day use of each product (cigarettes, refillable e-cigarettes, disposable e-cigarettes, hookah, cigars [including cigarillos and little cigars], and smokeless tobacco) was measured by the question, "During the past 30 days, have you used [product]?" Past 30-day use was a dichotomous measure (Yes/No coded as 1/0 respectively). The survey included pictures of the tobacco products. To measure frequency of use, participants were asked, "On how many of the last 30 days have you used such a product?" Frequency of use was modelled per every five days; i.e., the number of days used (range: 0–30) was divided by five to create a scaled variable (range: 0–6) and each unit of the scaled variable represented five days of use in the past 30 days Outcomes: Depressive symptoms were measured with the Center for Epidemiologic Studies Depression 10 scale (CES-D-10), a 10-item measure. Eight items asked about the frequency of a depressive symptom within the past seven days and were scored from 0 "rarely (less than 1 day)" to 3 "most of the time (5-7 days)." Two items asked about feeling hopeful or happy and were reverse coded. The scores were added to form a summary score with higher scores indicating greater frequency of depressive symptoms. The association between frequency of tobacco product use (cigarettes, e-cigarettes, hookah, cigars, and smokeless) and depressive symptoms based on within-person comparisons from a young adult cohort with six waves of data from October 2014 through June 2017. Further, the association between e-cigarette type (i.e., refillable and disposable e-cigarettes) and depressive symptoms is examined, as well as dual use of cigarettes with another tobacco product. The authors concluded, following separate examination of used refillable and disposable e-cigarettes, that the results did not provide evidence of a

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		different association for each type of e-cigarette when cigarettes were not also used. Dual use of cigarettes with another product was associated with higher depressive symptoms for most product combinations. However, infrequent dual use of disposable e-cigarettes and cigarettes may not be associated with depressive symptoms.[298] Device and products: Not reported
McMillen *et al.*[290] 2019	Harm	The authors reported on the relationship between **e-cigarette use and future cigarette initiation** among never-smokers, and relapse among former smokers. Distant former combustible cigarette smokers who reported e-cigarette past-30- Age mean (SD): 18 to 35 plus. Sex: 3,737 males, 4,348 females. Country: USA Data source: Population Assessment of Tobacco and Health Study Population size: 26,446 (Subpopulation 8085 reported on in this paper) Data collection period: 2 waves: 2013-2014 (baseline) and 2014-2015 (1-year follow-up) E-cigarette, smoking and other related status: In wave 1, respondents were asked, “Have you ever smoked a cigarette, even 1 or 2 puffs?” Respondents who replied yes were asked, “Do you now smoke cigarettes every day, some days, or not at all?” and “How many cigarettes have you smoked in your entire life?” Then all respondents who reported having ever smoked a combustible cigarette and who no longer smoked at all were asked, “About how long has it been since you completely quit smoking cigarettes?”. The authors defined distant former combustible cigarette smokers as adults who reported having ever smoked a combustible cigarette, having smoked equal to or more than 100 combustible cigarettes in their lifetime, no longer smoking combustible cigarettes, and having quit smoking combustible cigarettes equal to more than 5 years before completing the survey (n = 2322). The authors defined never combustible cigarette smokers as adults who had never smoked a combustible cigarette, even 1 or 2 puffs Outcomes: day use (9.3%) and e-cigarette ever users (6.7%) were significantly more likely than never users (1.3%) to have relapsed to current combustible cigarette smoking at follow-up (p<0.001). Baseline never-smokers who reported e-cigarette past-30-day use at follow-up (25.6%) and ever use (13.9%) were significantly more likely than those who had never used e-cigarettes (2.1%) to have initiated combustible cigarette smoking (p<0.001). Adults who reported past-30-day e-cigarette use (7.0%) and ever e-cigarette use (1.7%) were more likely than those who had never used e-cigarettes (0.3%) to have transitioned from never-smokers to current combustible cigarette smokers (p<0.001). E-cigarette use predicted combustible cigarette smoking in multivariable analyses controlling for covariates.[290] Device and products: Not reported
Soar *et al.*[293] 2019	Harm	The authors examined the relationship, in **exclusive vapers**, of levels of **nicotine intake** over time as nicotine e-liquid concentrations are reduced, i.e. **nicotine absorption** from e-cigarettes over a 12-month period. Age: the mean age was 43.81 (SD=9.19) years, Sex: 70% were male (n=19) Country UK. Ethnicity: 85% (n=23) were white British Data source: Recruited via social media (e.g. Twitter, Facebook) or were known to the authors from participation in other research studies

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		Population size: 32 Data collection period: Baseline and a 12 month follow up point (between June 2015 and March 2017) E-cigarette, smoking and other related status: 32 exclusive electronic cigarette users (i.e. did not also smoke or use nicotine in any other form) Outcomes: Paired samples t-test indicated a significant reduction in the strength of e-liquid (mg/mL consumed over the 12 month period [t(26)=2.32, p=.03 95% CI [0.45,7.38] and a significant increase in daily e-liquid consumption (mL), [t(22)=−2.51, p=.02] 95% CI[−4.38,2.51]. Cotinine levels increased slightly over the 12 month period but this change was not statistically significant [t(24)=−1.21, p=.24], [CI -121.76-31.96]. self-reported nicotine concentrations in e-liquid declined significantly over time whilst volume of e-liquid consumed significantly increased. There was no change (and even a slight increase over time) in salivary cotinine levels. it therefore appears that whilst vapers reduce the nicotine concentration of their e-liquid, this has no effect on their nicotine intake since levels of nicotine absorption remain stable The authors concluded that although the sample of experienced vapers reduced the concentration of nicotine in their e-liquid over time, they maintained their nicotine intake, possibly through self-titration via more intensive puffing. Findings suggest that there may be little benefit in reducing nicotine e-liquid concentration, since this appears to result in higher e-liquid consumption, which may incur both a financial and health cost.[293] Device and products: Nicotine e-liquid concentration (mg/mL) mean (SD): Baseline: 13.83 (8.53); 12 months: 9.91 (6.48) Daily liquid consumption (mL) mean (SD): Baseline: 4.44 (2.86); 12 months: 6.84 (6.45) Device Type mean (SD): Baseline: 2nd Generation n=1 (3.7), 3rd Generation n=17 (63.0), 3rd Generation & Sub-ohming n=8 (29.6). 12 months: 2nd Generation n=2 (7.4), 3rd Generation n=13 (48.1), 3rd Generation & Sub-ohming n=11 (44.4).
Wiernik *et al.*[296] 2019	Harm	The authors reported on the relationship **between e-cigarette use and depressive symptoms** in smokers and former smokers. Age: 18 to 69 years at cohort inception. For the longitudinal analysis mean age (SD) was 49.3 (13.1) years. Sex: For the longitudinal analysis 45.4% of subjects who were included were male Country: France Data source: French Constances cohort. The Constances cohort includes volunteers randomly selected from French adults who are covered by CNAMTS (Caisse nationale d'assurance maladie des travailleurs salaries), which is the national health insurance of>85% of the French population. Recruitment of participants began mid-2012 and is still ongoing. Questions about e-cigarette were first introduced in the 2013 follow-up questionnaire, then every year and in the inclusion questionnaire from 2015 onwards. For cross-sectional analyses, the study population was composed of all subjects included from January 2015 to December 2016, without missing data for selected variables. For longitudinal analyses, the study population consisted of all subjects included from February 2012 to December 2014, with at least one follow-up questionnaire without missing data for e-cigarette current use

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers dependency and abuse liability
		as well as for depressive symptoms, age, sex, years of education and tobacco smoking status at baseline. Population size: 35,337 for cross sectional analysis, 30,818 for longitudinal analysis Data collection period: February 2012 to December 2016. For the longitudinal analysis the mean (SD) follow-up duration was 1.88 (0.65) years E-cigarette, smoking and other related status: ever and current e-cigarette use as well as the type of device used (i.e. disposable or rechargeable) were reported at study baseline. Participants were categorized into the following categories: never users, ex-users and current users of e-cig. Furthermore, nicotine concentration in mg/mL was collected at baseline in four categories: 0 (i.e. e-liquid without nicotine) ;<6; 6–12; ≥13. Current e-cigarette use was also reported at follow-up, regardless of the date of inclusion. Outcomes: Cross-sectional and longitudinal associations were examined in this study group. Depressive symptoms were positively associated with e-cigarette use in both cross-sectional and longitudinal analyses with a dose-dependent relationship. In addition, nicotine concentration and depressive symptoms were positively associated. In longitudinal analyses (n=30,818), depressive symptoms at baseline were associated with current e-cigarette use at follow-up (2.02 [1.72–2.37]) with a similar dose-dependent relationship. These associations were mainly significant among smokers or former smokers at baseline. Furthermore, among smokers at baseline, depressive symptoms were associated with dual consumption at follow-up (1.58 [1.41–1.77]), whereas among former smokers, they were associated with either smoking only (1.52 [1.34–1.73]) or e-cigarette use only (2.02 [1.64–2.49]), but not with dual consumption (1.11 [0.73–1.68]) at follow-up The authors concluded that depressive symptoms were positively associated with e-cigarette use in both cross-sectional and longitudinal analyses with a dose-dependent relationship. In addition, nicotine concentration and depressive symptoms were positively associated.[296] Device and products: For participants included from January 2015 to December 2016, ever and current e-cigarette use as well as the type of device used (i.e. disposable or rechargeable) were reported at study baseline. Participants were categorized into the following categories: never users, ex-users and current users of e-cig. Furthermore, nicotine concentration in mg/mL was collected at baseline in four categories: 0 (i.e. e-liquid without nicotine);<6; 6–12;≥13. Current e-cigarette use was also reported at follow-up, regardless of the date of inclusion.

Table 75: Longitudinal cohort study papers on cardiovascular disease, benefits or harms

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers cardiovascular disease
Polosa *et al.* [299] 2016	Harm, but less harmful than tobacco cigarettes	The authors reported on the **relationship between smokers** with a diagnosis of **hypertension** and those who quit or reduced tobacco consumption by **switching to e-cigarettes**, and long-term improvement in resting blood pressure and in level of blood pressure control. Age years (SD): E-Cigarette Group 53.5 (+/-6.3) Control Group 54.2 (+/-7.5) Sex: E-Cigarette Group 26 M, 17 F Control Group 24 M, 22 F Total 50 male, 39 females Country: Italy

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers cardiovascular disease
		Data source: A medical records review of patients with hypertension was conducted to identify patients reporting regular daily use of e-cigarettes on at least two consecutive follow-up visits. Data from a second group of age-, sex-matched patients who reported to be regular smokers on at least two consecutives follow-up visits was included as a reference group. Patients in both study groups had to have similar weight (<5 kg) and systolic BP (<10 mmHg) fluctuations between pre-baseline and baseline visits. Data from four visits were collected and analysed. At outpatient clinic visit patients were assessed for smoking history, systolic and diastolic blood pressure, heart rate, and body weight. Any patients with a known cause of secondary hypertension were excluded. The forty-three patients in the electronic cigarette group (26 male, 17 females) reported regular daily use of e-cigarettes at two consecutive follow-ups. E-cigarette use ranged from 10 to 14 months, with 36/43 (83.7%) patients using them for more than a year. Population size: A total of 89 regular smokers with a diagnosis of hypertension and on anti-hypertensive drugs at baseline. E-Cigarette Group (n = 43). Control Group (n = 46). Data collection period: Year not reported. Data from four visits were collected and analysed: specifically, data from chart review immediately preceding baseline visit, baseline visit and two consecutive follow-up visits (follow-up visit 1 and 2). Pre-baseline visits were carried out at 6–12 months prior to baseline visits. Follow-up visit 1 and 2 were carried out at 6 (+/-1) and 12 (+/-2) months after baseline visit E-cigarette, smoking and other related status: hypertensive smokers who quit or reduced substantially their tobacco consumption by switching to e-cigarettes. Patients reporting regular daily use of e-cigarettes on at least two consecutive follow-up visits were eligible to be included in the study Outcomes: The routine approach to anti-hypertensive treatment was employed and included a combination of drugs that work on different pathophysiological pathways in order to maximize blood pressure control. Where appropriate diuretics, vasodilators, sympatholytics, and renin-angiotensin-aldosterone system blockers are prescribed. Changes to medications were made after review of both blood pressure office measurements and blood pressure home readings and were recorded. Self-reported adherence to medications was assessed at each visit. Changes in smoking behaviour and patterns of e-cigarette use: A marked reduction in conventional cigarette consumption was observed in regular daily e-cigarette users, their mean (+/-SD) cigarettes/day use decreasing from 20.2 (+/-5.0) at baseline to 2.6 (+/-2.9) at follow-up visit 1 and to 1.8 (+/-2.0) at follow-up visit 2, respectively ($p < 0.001$ for both visits). No significant reduction in conventional cigarette consumption was observed in the reference group. Dual usage was reported by 23/43 (53.5%) patients at follow-up visit 1 and 22/43 (51.2%) at follow-up visit 2, respectively. A significant reduction in conventional cigarette consumption was also observed in dual users, with their mean (+/-SD) cigarettes/day use decreasing from 21.5 (+/-6.9) at baseline to 4.8 (+/-2.3) at follow-up visit 1 and to 3.7 (+/-1.1) at follow-up visit 2, respectively ($p < 0.001$ for both visits). More than a 75% reduction from baseline in cigarettes/day consumption was reported by 14/23 (60.9%) dual users at follow-up visit 1 and by 17/22 (77.3%) at follow-up visit 2, respectively. A significant reduction in median systolic blood pressure ($p < 0.001$) and diastolic blood pressure ($p = 0.006$) from baseline was observed at follow-up visit 2 in the e-cigarette group. In contrast, no significant change in blood pressure was observed in the reference group. The observed reductions in systolic blood pressure and diastolic blpod pressure were significant ($p < 0.001$, both for both measures) when comparing the e-cigarette group to the reference group at 12 months. In dual users (following

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers cardiovascular disease
		subgroup analysis) apart from reduced cigarette consumption and systolic blood pressure at 12 months—no significant changes from baseline measures were observed[299] The authors concluded that regular e-cigarette use may aid smokers with arterial hypertension in reducing or abstaining from cigarette smoking, with only trivial post-cessation weight gain (a finding reported on in the paper). The reduction in cigarette smoking and weight and the taking up of e-cigarettes resulted in improvements in systolic and diastolic blood pressure as well as better blood pressure control.[299] Device and products: Not reported
Polosa *et al.*[300] 2017	No harm or benefit	The authors reported-on **cardiovascular and respiratory health outcomes** blood pressure, heart rate, body weight, lung function, respiratory symptoms, fractional exhaled breath nitric oxide (FeNO), exhaled carbon monoxide (eCO), and high-resolution computed tomography of the lungs. Age: mean (+/-SD) age of 29.7 (+/-6.1) years. Sex: Male 11; Female 5. Country: Italy Data source: Adult e-cigarette users (≥18 years old) were identified amongst a pool of regular vape shops customers. Vape shop owners who helped in a previous study were instructed to ask their regular clients a few questions about smoking history and e-cigarette use patterns. Population size: 16 Data collection period: June 2013 to September 2013 and data collection completed in March 2017. Aside from the baseline visit three additional follow-up visits were scheduled yearly for up to 3.5 years; follow-up visits 1 (F/up1), 2 (F/up2) and 3 (F/up3) were carried out at 12 (+/-1), 24 (+/-2) and 42 (+/-2) months after baseline visits, respectively E-cigarette, smoking and other related status: Customers who had never smoked or who reported having smoked less than 100 cigarettes in their lifetime were defined as never smokers and considered for inclusion. They also had to be daily e-cigarette users of ≥3 months. Age- and sex-matched non-smoking controls (and not using e-cigarettes) were selected from hospital staff and included as a reference (control) group. Vapers recruited into the study had generally a short duration of regular e-cigarette use prior to entering the study (on average 8 months) and vaporized, on average, only a modest amount of e-liquid (about 4 ml/die), Outcomes: No impairment in the health measures evaluated in any of the e-cigarette users in the study were reported. In a small sample of young-adult never-smoking, daily e-cigarette users who were carefully followed for approximately 3½ years, the authors found no decrements in spirometric indices, development of respiratory symptoms, changes in markers of lung inflammation in exhaled air or findings of early lung damage on high-resolution computed tomography, when compared with a carefully matched group of never-smoking non-e-cigarette users. Even the heaviest e-cigarette users failed to exhibit any evidence of emerging lung injury as reflected in these physiologic, clinical or inflammatory measures. Moreover, no changes were noted in blood pressure or heart rate. Since the e-cigarette users who we studied were never smokers, potential confounding by inhalation of combustion products of tobacco were obviated. The authors concluded that although it cannot be excluded that some harm may occur from e-cigarettes at later stages of the e-cigarette users life, this study did not demonstrate any health concerns associated with long-term use of e-cigarettes in relatively young users who did not also smoke tobacco.[300]

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers cardiovascular disease
		Device and products: Not reported
Michaels *et al.*[301] 2018	Harm	The authors examined nicotine replacement therapy (including **e-cigarettes) as a safe alternative to smoking** in plastic surgery patients. Age: Average age in years was: non-nicotine users (48.5), smokers remaining abstinent (48.5), smokers (49.2), and non-smoker nicotine users Sex: Not reported. Country: USA Data source: All patients undergoing major surgery at a single outpatient ambulatory day surgery centre for a 5-year period. Population size: Four hundred seventy patients were included in the study. Patient count in each group was group A n = 380, group B n = 48, group C n = 32, and group D n = 10. Data collection period: 1/1/2012-12/2016. Data were compiled in 2017. Patients were followed by the surgeons for 6 weeks to monitor for postoperative complications. E-cigarette, smoking and other related status: Patients were divided into 4 groups: never smoked (group A), quit smoking with negative urine test (group B), continued to smoke (group C), and quit smoking with positive urine test (group D). Patient count in each group was group A n = 380, group B n = 48, group C n = 32, and group D. tobacco usage and nicotine replacement methods were self-reported and individual usage habits and doses of the patients were not captured. Outcomes: The complications found were wound dehiscence, flap loss (both major and minor), capsule formation (Baker 3 or 4), hematoma, and seroma. Measures of urine cotinine, a nicotine metabolite were assessed. Nicotine replacement carries similar risks as continued smoking and is not as safe as abstinence in the perioperative period in plastic surgery patients. Importantly, patients who stopped smoking for the surgery had equivalent risk for postoperative complications as patients who had never smoked. However, it should be noted that differentiation between the various nicotine replacement therapies, specifically e-cigarettes could not be assessed. The authors concluded that nicotine replacement using e-cigarettes carries similar risks as continued smoking and is not as safe as abstinence in the perioperative period in plastic surgery patients. Importantly, patients who stopped smoking for the surgery had equivalent risk for postoperative complications as patients who had never smoked.[301] Device and products: Not reported

Table 76: Longitudinal cohort study papers on respiratory diseases, benefits or harms

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
Polosa *et al.*[302] 2014	Harm, but less harmful than tobacco cigarettes	The authors undertook a retrospective review of **changes in** spirometry data, airway hyperresponsiveness, **asthma exacerbations,** and subjective asthma control in smoking asthmatics who **switched to regular e-cigarette use**. Age: years 37.8 (±12.3) Sex: 11 male, 7 females Country: Italy Data source: A medical records review of patients with hypertension was conducted to identify patients reporting regular daily use of e-cigarettes on at least two consecutive follow-up visits. Data from four visits were collected and analysed: data from chart review immediately preceding baseline visit, two consecutive follow-up visits (follow-up visit 1 and 2). Pre-baseline visits

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
		were carried out at 6–12 months prior to baseline visits. Follow-up visit 1 and 2 were carried out at 6 (+/-1) and 12 (+/-2) months after baseline visit. Population size: 18. Data collection period: September 2012 to December 2013 E-cigarette, smoking and other related status: At outpatient clinic visit patients were assessed for smoking history, systolic (SBP) and diastolic blood pressure, heart rate, and body weight. Any patients with a known cause of secondary hypertension were excluded. The patients in the electronic cigarette group reported regular daily use of e-cigarettes at two consecutive follow-ups. E-cigarette use ranged from 10 to 14 months, with patients using them for more than a year. Of the 18 electronic cigarette users identified all were former tobacco smokers of about 20 conventional tobacco cigarettes/day. There were 10 single and eight dual users by the time of their most recent follow-up visit (follow-up visit 2). All dual users smoked ≤5 conventional tobacco cigarettes/day. All patients initially switched to a cigarette-like model, but the majority went on to adopt a personal vaporizer. Duration of regular electronic cigarette use ranged from 10 to 14 months, with twelve patients using them for more than a year. All patients took a stable dose of inhaled corticosteroids, long-acting (LABA) and on-demand short-acting β2 agonist as well as on-demand short-acting β2 agonist throughout the observation period. None of the patients included had ever received a significant modification in anti-asthma therapy from their pre-baseline visit. Outcomes: lung function, bronchial hyperresponsiveness (BHR) or Juniper's Asthma Control Questionnaire scores, spirometry with parameters of forced expiratory flow in 1 second (FEV1), forced vital capacity (FVC), expiratory ratio (%FEV1/FVC) and forced expiratory flow at the middle half of the FVC (FEF25%-75%); and (iv) in some subjects bronchial provocation tests assessing Airway Hyperresponsiveness (AHR) with methacholine were also conducted as previously described The authors reported improvements in asthma control, airway hyperresponsiveness, and pulmonary function in 18 asthmatic smokers who quit or dramatically reduced their tobacco consumption by switching to e-cigarettes.[302] Device and products: All patients initially switched to a cigarette-like model, but the majority went on to adopt a personal vaporizer
Polosa *et al.*[303] 2016b	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between persisting long-term **benefits of smoking abstinence and reduction in asthmatic smokers who have switched to e-cigarettes**. Age: 38.0 (+/- 12.3). Sex: 10 males, 6 females. Country: Italy Data source: A medical records review of patients with hypertension was conducted to identify patients reporting regular daily use of e-cigarettes on at least two consecutive follow-up visits. An asthma cohort of adult daily electronic cigarette users was identified. Data from four visits were collected and analysed: data from chart review immediately preceding baseline visit, baseline visit and two consecutive follow-up visits (follow-up visit 1 and 2). Pre-baseline visits were carried out at 6–12 months prior to baseline visits. Follow-up visit 1 and 2 were carried out at 6 (+/-1) and 12 (+/-2) months after baseline visit. Population size: 16. Data collection period: October 2013 to January 2015 E-cigarette, smoking and other related status: Before switching to e-cigarettes: single users n=10 reported smoking pack years of 14.0 (SD +/- 2.8),

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
		dual users n=6 reported smoking pack years 29.8 (SD +/- 11.1). At 24-month follow-up all patients reported using 1.5 (SD +/-1.95) cigarettes per day. Outcomes: Juniper's Asthma Control Questionnaire (ACQ) score, number of exacerbations from the previous follow up visit (an asthma exacerbation was defined as an increase in respiratory symptoms requiring a short course of oral or parenteral corticosteroids), simple spirometry with parameters of forced expiratory flow in 1 second (FEV1), forced vital capacity (FVC), and forced expiratory flow at the middle half of the FVC (FEF25%-75%); and in some subjects bronchial provocation tests assessing airway hyperresponsiveness (AHR) with methacholine. Smoking abstinence was defined as complete self-reported abstinence from tobacco smoking (not even a puff) since the previous study visit. This was biochemically verified at F/up 3 byexhaled carbon monoxide levels of ≤7 ppm. Asthmatic e-cigarette users in this category are classified as Quitters (Single users). Smoking reduction was defined as sustained self-reported reduction (at least >50%) in the number of cigarettes per day from baseline. Asthmatic electronic cigarette users in this category are classified as Reducers (Dual users). E-cigarette users who were not categorized in the above categories were classified as Relapsers. The authors concluded that regular e-cigarette use ameliorates asthma outcomes, that these beneficial effects may persist in the long term, that similar benefits could also be noted in dual users, and that regular e-cigarette use was well tolerated.[303] Device and products: For all patients, first-time purchase was a "cig-alike" e-cigarette model, but the majority went on to adopt refillable "pen-like" e-cigarettes. Duration of regular e-cigarette use ranged from 20 to 26 months, with ten patients using them for at least 2 years. All participants were using standard refillable e-cigarettes by the end the study. The preferred nicotine strength of their e-liquid was 9 mg/ml and 18 mg/ml, which was consumed by 62.5% (10/16) and 18.8% (3/16) of e-cigarette users respectively. Most of the participants consistently preferred tobacco flavours over other flavours at final follow up visit.
Polosa *et al.*[304] 2016c	Harm, but less harmful than tobacco cigarettes	The authors reported their evidence for **harm reduction in smokers with chronic obstructive pulmonary disease who switch to using e-cigarettes.** Sex: Electronic-cigarettes cases 20 males, 4 females comparable controls 21 males, 3 females. Country: Italy Data source: A medical records review of patients with hypertension was conducted to identify patients reporting regular daily use of e-cigarettes on at least two consecutive follow-up visits. Data from four visits were collected and analysed: data from chart review immediately preceding baseline visit, data from the baseline visit and two consecutive follow-up visits (follow-up visit 1 and 2). Pre-baseline visits were carried out at 6 to 12 months prior to baseline visits. Follow-up visit 1 and 2 were carried out at 6 (+/-1) and 12 (+/-2) months after baseline visit. Population size: Chronic obstructive pulmonary disease e-cigarettes users n=24 and comparable controls n=24 Total 48 Data collection period: September 2013 to December 2015 E-cigarette, smoking and other related status: Patients reporting regular daily use of e-cigarettes (and if at all conventional tobacco cigarettes) at least two follow-up visits over a 24-months period were eligible for inclusion. A second group of age- and sex-matched chronic obstructive pulmonary disease control patients reporting to be regular smokers (and not using e-cigarettes) over the

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
		same observation period was selected from four participating clinics as a reference (control) group. Outcomes: The primary outcomes of interest were: a) reduction in cig/day consumption; and b) number of exacerbations in the previous 12 months at each of the visits and how they may have changed over the 24-month period in the e-cigarettes group compared to the control group. Secondary outcomes of interest were changes from baseline to the final follow-up visit in: lung function; chronic obstructive pulmonary disease Assessment Test (CAT) scores, and 6-minute walk distance (6MWD). In addition, changes in the relative proportion of chronic obstructive pulmonary disease GOLD stages throughout the 24-months observation period were reported for both study groups as well as the change in mean FEV1 from baseline to F/up2. The authors concluded that a marked reduction in cigarette consumption was observed in e-cigarette users. A significant reduction in chronic obstructive pulmonary disease exacerbations was reported in the chronic obstructive pulmonary disease e-cigarette user group, with their mean (±standard deviation) decreasing from 2.3 (±1) at baseline to 1.8 (±1; p=0.002) and 1.4 (±0.9; p<0.001) at follow-up visit 1 and follow-up visit 2, respectively. A significant reduction in chronic obstructive pulmonary disease exacerbations was also observed in e-cigarette users who also smoked conventional combustible tobacco cigarettes (i.e. dual users). Chronic obstructive pulmonary disease symptoms and ability to perform physical activities improved statistically in the e-cigarettes group at both visits, with no change in the control group. Age: Electronic-cigarettes users 66.9 (±6.7) chronic obstructive pulmonary disease controls 65.3 (±5.5)[304] Device and products: Not reported
Bowler *et al.*[305] 2017	Harm	The authors reported on the relationship between **e-cigarette use** in USA adults at risk for, or with, **chronic obstructive pulmonary disease**. Age: COPD Gene group aged 45 to 80 years, SPIROMICS group age 40 to 80 years. Sex: COPD Gene: Never e-cigarette use (N = 3,117) Current e-cigarette use (N = 127) Former e-cigarette use (N = 291) SPIROMICS Never e-cigarette use (N = 888) Current e-cigarette use (N = 55) Former e-cigarette use (N = 117) Country USA Data source: The NIH-sponsored multicentre COPD Gene study includes 10,294 subjects enrolled from 2008 to 2011 who were self-reported non-Hispanic white or African-American, and with a history of at least 10 pack-years of conventional cigarette smoking (N = 10,192) or no conventional cigarette smoking (≤ 1 pack-year lifetime; N = 102). The NIH-sponsored multicentre SPIROMICS is a cohort study that enrolled 2,982 subjects between November 2011 and January 2015. Inclusion criteria included age 40 to 80 years and at least 20 pack-years of conventional cigarette smoking (N = 2,780) or never tobacco smokers (N = 202). Population size: COPD Gene (N = 3,536) and SPIROMICS (N = 1,060). In COPD Gene, conventional cigarette smoking was assessed at both baseline and 5-year follow-up visit. In SPIROMICS there was not a sufficient number of subjects who had both long-term follow-up visits (> 1 year) and e-cigarette questionnaire data; thus data from these subjects was cross-sectional and not reported here. Data collection period: 2010 to 2016 E-cigarette, smoking and other related status: A total of 419 (12%) subjects in COPD Gene and 172 subjects (16%) in SPIROMICS reported ever using e-

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
		cigarettes. However, only 128 of 3536 (4%) and 55 of 1060 (5%) were currently using e-cigarettes at the time of study visits, with no significant difference in the percentage of subjects currently using e-cigarettes at the time of the survey 2014 to 2016. The duration of e-cigarette use in current smokers was longer in former e-cigarette users, but this difference was significant only in the SPIROMICS cohort. Outcomes: In both cohorts, COPD was defined as post-bronchodilator ratio of forced expiratory volume in one second (FEV1) to forced expiratory volume (FVC) < 0.70. Electronic-cigarette use was associated with worse pulmonary-related health outcomes, but not with cessation of smoking conventional tobacco cigarettes. The authors concluded that they could find no evidence supporting the use of e-cigarettes as a harm reduction strategy among current smokers with, or at risk for, chronic obstructive pulmonary disease.[305] Device and products: Not reported
Flacco *et al.*[306] 2019	Harm	The authors reported on the relationship between **e-cigarettes and a range of possibly smoking-related diseases** – such as chronic obstructive pulmonary disease, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischaemia or stroke, and any cancer – and changes in tobacco use. Age: 30-75 years. Sex: 56 >3% males. County: Italy Data source: Potential participants were recruited via general practitioners, e-cigarette shops, internet advertisements, and social networks Population size: 228 e-cigarette users (all ex-smokers), 471 tobacco smokers, 216 dual users. Data collection period: 2013 to 2017. The follow-up period was proposed to continue up to 72 months. The results reported here are after four years follow-up. E-cigarette, smoking and other related status: smokers of >=1 tobacco cigarette/day (tobacco smokers); users of any type of e-cigarette inhaling >=50 puffs weekly (e-cigarette users); users of both tobacco and e-cigarette (dual users). At recruitment (2013) recruited adults (30-75 years) who were: (a) smokers of ≥ 1 tobacco (only) cigarette daily for ≥ 6 months (tobacco smokers); (b) users of any type of e-cigarette for ≥ 6 months (e-cigarette users); (c) users of both tobacco and e-cigarette for ≥ 6 months (dual users). Outcomes: possibly smoking-related diseases (i.e. chronic obstructive pulmonary disease, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer.; validated through hospital discharge data or visit in 62.6% of the sample); 4-year tobacco abstinence; number of tobacco cigarettes/day. More specifically effectiveness outcomes were: (a) the rate of quitting of all products (either tobacco and/or e-cig, for >30 days); (b) the rate of abstinence/cessation from tobacco smoking at 48 months; and (c) the change in the daily number of tobacco cigarettes. Health outcomes were: (a) the rate of possibly smoking-related diseases; and (b) the change in self-reported health (assessed through the final item of the Italian version of the EuroQol EQ-D5L). Data were collected by phone and/or internet, and carbon monoxide levels tested in 50% of those declaring tobacco abstinence. A possibly smoking-related diseases was observed in 73 subjects (8.0%). No differences emerged across groups in possibly smoking-related diseases rates, with negligible variations in self-reported health. Of e-cigarette users, 63.6% remained tobacco abstinent; dual users and tobacco smokers showed non-significantly

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers respiratory diseases
		different rates of tobacco (33.8% vs. 26.8%) and all-product (20.2% vs. 19.4%) cessation, and a similar decrease in cigarettes/day. Almost 40% of the sample switched at least once (tobacco smokers: 17.2%; dual users: 81.9%). The authors concluded that after 4 years, a scarce, non-significant harm reduction was observed among e-cigarette users and dual users of e-cigarettes and conventional tobacco cigarettes. The complete switch to e-cigarettes may help tobacco quitters remain abstinent, but e-cigarette use in addition to tobacco did not increase the likelihood of smoking cessation or reduction. The rates of smoking-related diseases were similar in e-cigarette users, dual users (those who used both e-cigarettes and conventional tobacco cigarettes), and conventional tobacco cigarette smokers.[306] Device and products: Not reported

Table 77: Longitudinal cohort study papers on oral diseases, benefits or harms

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers oral diseases
Tatullo *et al.*[307] 2016	Harm, but less harmful than tobacco cigarettes	The authors reported on the **changes in periodontal health in individuals** who had ceased **tobacco cigarette** consumption and had started to use **e-cigarettes**, and a self-assessed need to smoke combustible cigarettes. Age: average age 31± 9. Sex: 89 men and 21 women. Country Italy Data source: Clinical observational study at the Unit of Periodontology and Oral Hygiene of Calabrodental Clinic. Population size: n=110 Data collection period: This study was conducted for 120 days on each patient. Clinical examinations were performed at 3 different check-points: T0 (baseline), T1 (after 60 day), and T2 (after 120 days). The 1st selection was performed by choosing those subjects which started to use e-cigarette approximately from 4±1 month, before the start of the study. Smokers were divided into 2 groups, according to the number of years of smoking by each of them: group 1 (less than 10 years of tobacco smoking), group 2 (more than 10 years of tobacco smoking). All subjects were asked to abstain from tobacco cigarettes for the entire duration of the study. No year of study provided. E-cigarette, smoking and other related status: All the recruited patients, who switched to the e-cigarettes, reported that they have previously smoked only combustible cigarettes with high amount of nicotine (among 0.8–1mg per cigarette). All patients included in the study stated that they use e-cigarettes with an average content of 0.25mL of liquid containing a total amount of nicotine equivalent to 18mg: each cycle of use of the e-cigarette contains on average 4.5mg of nicotine, although the calculation should not consider the dispersed nicotine part, equal to about half of the basic content. The subjects enrolled in the study said they had smoked in the past an average of 20 cigarettes a day, absorbing an average of 16mg of nicotine per. day. With the e-cigarette, if subject smokes the same number of cigarettes in a day it would be absorbed approximately 7mg of nicotine. Outcomes: The oral cavity was divided in 4 areas: upper right and upper left jaw, lower right and lower left jaw. Each patient underwent an oral examination to investigate the following parameters: plaque index, periodontal bleeding index, and papillary bleeding index. Patients also completed a self-assessment on: general health status; smell perception; taste perception; frequency of respiratory diseases; and need to smoke. The authors stated that their observations revealed an interesting, growing trend, relating to plaque index, periodontal bleeding index, and papillary

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers oral diseases
		bleeding index, in the 110 subjects considered in this study. They reported a constant reduction of bacterial plaque on teeth surfaces from baseline at T0 to the end of the observational period at T2. More precisely, group 1 (less than 10 years smoking) subjects showed a homogeneous presence of a thin film of plaque at T0, which visibly decreased towards T1 until it completely disappeared in all of the group 1 subjects at T2. The result was more marked in group 2 subjects (more than 10 years smoking), and was characterised by a huge presence of plaque at T0. The authors also noted that many patients had reported an interesting reduction in the need to smoke.[307] Device and products: Not reported
ALHarthi *et al.*[308] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the impact of **cigarette smoking, e-cigarette use, and non-smoking** on **dental and periodontal health**: full-mouth plaque index, bleeding on probing, clinical attachment loss, and probing depth were measured at baseline and at 3 and 6 months after full-mouth ultrasonic scaling (without root surface debridement). The numbers of missing teeth were also recorded. Age (range) years: 25 to 60 years mean (SD) cigarette smokers 36.4 ± 2.8, e-cigarette vaping participants 32.5 ± 4.8, non-smoking individuals 32.6 ± 3.5 Sex: All males. Country: Saudi Arabia. Data source: Clinic attendees Population size: cigarette smokers n=30, e-cigarette vaping participants n=28 non-smoking individuals n=31 Data collection period: June 2016 and February 2017 E-cigarette, smoking and other related status: Cigarette smokers: individuals who were smoking at least five cigarettes daily since at least 12 months, e-cigarette vaping participants: individuals without a previous history of tobacco usage who had been vaping exclusively e-cigarettes for at least 1-year, non-smoking individuals who reported to have never used any form of tobacco product Outcomes: full-mouth plaque index, bleeding on probing, clinical attachment loss, and probing depth and number of missing teeth The authors stated that a range of periodontal inflammatory parameters were worse in cigarette smokers than in individuals who vape e-cigarettes and in never-smokers following full-mouth ultrasonic scaling.[308] Device and products: Not reported
Atuegwu *et al.*[309] 2019b	Harm	The authors reported on the relationship between **e-cigarettes and periodontal disease**, specifically gum disease and bone loss around teeth. Age: 18 years of age or older. Sex: 8,791 males, 9,468 females. Country USA Data source: Population Assessment of Tobacco and Health study Population size: 18,259 persons with no history of gum disease at baseline and with full relevant data. 329 participants who reported longitudinal electronic nicotine product use, 8298 participants who reported non-longitudinal electronic nicotine product use and 9632 participants who reported never electronic nicotine product use. Data collection period: 12 September 2013 to 14 December 2014 (wave 1), 23 October 2014 to 30 October 2015 (wave 2), and 19 October 2015 to 23 October 2016 (wave 3). Three year follow up. E-cigarette, smoking and other related status: Regular electronic nicotine product users were participants who said yes to using “electronic nicotine products (such as e-cigarettes, vape pens, personal vaporizers and mods, e-

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers oral diseases
		cigars, e-pipes, e-hookahs and hookah pens) fairly regularly every day or some days. Longitudinal electronic nicotine product users were participants who were regular electronic nicotine product users in all the three waves of the PATH survey. Longitudinal conventional cigarette users were participants who have smoked more than 100 cigarettes in their lifetime and smoked every day or someday in all the three waves of the PATH survey. Outcomes: Participants with no history of gum disease who used electronic nicotine products regularly every day or some days for a year or more had increased odds of being diagnosed with gum disease, even after controlling for conventional cigarette smoking and other known risk factors. The participants who used electronic nicotine products also had an increased odds of reporting bone loss around teeth which is indicative of advanced periodontal disease. The odds were higher for participants who had a history of marijuana use or any illicit and non-prescribed drug use. The hypothesis in this study was that the use of electronic nicotine products would be associated with increased odds of gum disease and bone loss around teeth, even after controlling for use of conventional combustible tobacco cigarettes and other known risk factors. Sub-group analysis was performed to examine this association in participants who had a history of marijuana use and a history of illicit or non-prescribed drug use. The authors concluded that this was the case.[309] Device and products: Not reported

Table 78: Longitudinal cohort study papers on developmental and reproductive effects, benefits or harms

Author(s) year	Possible benefit or harm	Longitudinal cohort study papers developmental and reproductive effects
Cardenas *et al*.[310] 2019	Harm	The authors reported on the relationship between **e-cigarette use** in pregnant women and **risk of small-for-gestational-age births.** Age (range) years: 18 to over 28 years. Sex: All females. Ethnicity: Country: USA Data source: volunteers among patients seen at a prenatal clinic serving low-risk pregnant women (those without underlying medical conditions or co-morbidities and without antenatal complications) Population size: 248 pregnant women. Data collection period: April 2015 to May 2017 E-cigarette, smoking and other related status: current e-cigarette use among pregnant women most (75%) of which were also concurrent cigarette smokers. Status was assessed by self-report exposure to tobacco products and non-invasive biomarker assays Outcomes: birth weight and risk of small-for-gestational-age in 232 participants The authors concluded that e-cigarette use is associated with an increased risk of small-for-gestational-age births.[310] Device and products: Not reported

Appendix 5: Interventional trials papers by adapted Academies of Sciences framework headings for e-cigarettes

Table 79: Interventional trial papers on dependency and abuse liability, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
Eissenberg[320] 2010	No benefit	The authors reported on the relationship between **nicotine delivery and craving suppression**, heart rate, and subjective effects. Age mean years (SD): 29.8 (10.7). Sex: 11 males, 5 females Country: USA. Ethnicity: 8 non-white Duration of trial: Two hours Population size: 16 Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers naïve to e-cigarette. Mean cigarettes/day=18.5, SD=2.2 Intervention and research design: Participants were instructed to puff normally and then puffed ad libitum 10 times (30-s inter puff interval) from the product of the day (bout 1). At 5, 15, 30 and 45 minutes after the first puff, subjective measures were completed, and blood sampled. At time +60 minutes assessments were repeated, product was administered (bout 2), and identical subsequent assessments completed Outcomes: Plasma nicotine and 'craving for a cigarette/nicotine', heart rate The authors concluded that relative to a tobacco cigarette, 10 puffs from an e-cigarette with a 16 mg nicotine cartridge delivered little to no nicotine and suppressed cravings less effectively. Results on heart rate were not reported.[320] Device and products: Own brand cigarettes, sham smoking (puffing an unlit cigarette), 'NPRO' (NJOY, Scottsdale, Arizona, USA) with a 16 mg nicotine cartridge, or 'Hydro' (Crown Seven, Scottsdale, Arizona, USA) with a 16 mg nicotine cartridge. Cartridge flavour (menthol or regular) was chosen to match participant's preferred cigarette flavour. A new cartridge (within its expiration date) and a fully charged battery were used for each session.
Vansickel *et al.*[311] 2010	Benefit	The authors reported on the relationship between own-brand **cigarettes, two types of e-cigarette devices,** and a sham (unlit cigarette) with **plasma nicotine and carbon monoxide (CO) concentrations**, heart rate, and a range of subjective effects. Age years (SD): 18 to 55 years. Sex: Not reported. Country: USA Duration of trial: Four sessions. Eight-day interval between sessions Data source: men and women recruited from the Richmond, Virginia area USA Population size: 32. Year of data collection: Not reported E-cigarette, smoking and other related status: Participants smoked at least 15 cigarettes per day (mean, 22 cigarettes per day; SD, 8.8) Outcomes: Plasma nicotine and carbon monoxide concentration, heart rate, and subjective effects – from the Hughes and Hatsukami questionnaire were assessed. Subjective effects included anxious craving a cigarette depression/feeling blue, difficulty concentrating, drowsy, hunger, impatient, irritability/frustration/anger, restless, desire for sweets, urge to smoke). Direct effects of nicotine (confused, dizzy, headache, heart pounding, lightheaded, nausea, nervous, salivation, sweaty, weak). Direct effects of tobacco (satisfying, pleasant, taste good, dizzy, calm, concentrate, awake, reduce hunger, sick, taste

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		like own brand, feel like own brand, harsh as own brand, mild as own brand, smoke another cigarette RIGHT NOW) Own brand significantly increased plasma nicotine and CO concentration and heart rate within the first five minutes of administration whereas the devices tested (NPRO e-cigarette, Hydro e-cigarette, and sham smoking) did not Intervention and research design: four independent Latin-square ordered conditions that differed by product. Participants took 10 puffs at two separate times during each session The authors concluded that in acute testing conditions, neither of the e-cigarettes exposed users to measurable levels of nicotine or carbon monoxide, although both suppressed nicotine/tobacco abstinence symptom ratings.[311] Device and products: own brand cigarette, "NPRO" electronic cigarettes (NPRO e-cigarette; 18 mg cartridge), "Hydro"e-cigarettes (Hydro e-cigarette; 16 mg cartridge), or sham (unlit cigarette)
Dawkins *et al.*[323] 2012	Benefit for men	The authors reported on the relationship between **e-cigarettes and effects on desire to smoke, withdrawal symptoms, and cognition**. The study aimed to explore whether e-cigarettes can reduce desire to smoke and also reduce abstinence-related withdrawal symptoms over a 20-minute period. Age mean years (range): 28.8 (18 to 52). Sex: 43 males, 43 females. Country: UK Duration of trial: 20 minutes. Following abstinence from smoking for at least 1 hour, participants completed the Fagerstrom Test of Nicotine Dependence to assess six nicotine withdrawal symptoms: depression, irritability, anxiety, restlessness, hunger, poor concentration at baseline (T1), 5 (T2) and 20 (T3) minutes after using (or just holding) the electronic cigarette ad libitum for 5 minutes. Data source: Not reported. Population size: 86. Data collection year: Not reported E-cigarette, smoking and other related status: e-cigarette naive smokers Intervention and research design: Subjects were randomly allocated to either 18mg nicotine e-cigarette (nicotine), 0 mg e-cigarette (placebo; nicotine and placebo conditions administered single-blind) or just hold the e-cigarette (just hold) condition. Outcomes were assessed 20 minutes after exposure. Outcomes: Desire to smoke, Mood and Physical Symptoms Scale (MPSS) (depression, irritability, anxiety, restlessness, hunger, poor concentration), Letter Cancellation Task (a quick measure of attention/speed of processing and visual–spatial scanning ability) and the Brown–Peterson Working Memory. The authors concluded that desire to smoke and some aspects of nicotine withdrawal were significantly reduced 20 (but not 5) minutes after e-cigarette use; in this respect, the nicotine e-cigarette was superior to placebo in males but not in females. Nicotine derived via use of e-cigarettes also improved working memory performance, particularly at the longer interference intervals.[323] Device and product: The 'White Super' electronic cigarette was used (devices and cartridges supplied by The Electronic Cigarette Company) with a new tobacco flavoured cartridge for each participant.
Vansickel *et al.*[312] 2012	Benefit	The authors assessed the **abuse liability of e-cigarettes**. Age mean years (SD): 33.1 ± 11.8 . Sex: Not reported. Country: USA

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Duration of trial: Four sessions. Eight-day interval between sessions. Measures were assessed up to 30 minutes post intervention Data source: Not reported Population size: 20. Year of data collection Not reported: E-cigarette, smoking and other related status: Current tobacco cigarette smokers >=15 cigarettes per day. Intervention and research design: Latin square. Participants completed four 4-hour-long sessions that were separated by at least 48 hours and were preceded by at least 12 hours of objectively verified cigarette abstinence. The first session was a 'sampling' session that familiarized participants with the e-cigarette. The remaining three sessions were randomly ordered 'choice' sessions that differed by the options provided. Outcomes: Plasma nicotine, cardiovascular measures, questionnaire of smoking urges brief, nicotine/tobacco abstinence symptoms The authors concluded that e-cigarettes can deliver clinically significant amounts of nicotine and reduce cigarette abstinence symptoms. In addition, they appear to have lower potential for abuse relative to traditional tobacco cigarettes.[312] Device and product: The 'Vapor King' (KR808 model) automatic e-cigarette was used in this study[450] It was chosen based on suggestions from experienced EC users who reported that this model would be acceptable to new users as it resembles a cigarette and would produce a consistent vapor. The 'Vapor King' consists of a rechargeable 3.7-volt battery and air flow sensor with a lighted display end; a disposable cartridge ('cartomizer') consisting of a metal threading (to fit securely onto the battery), heating element and wicking that is saturated with nicotine solution. 'WOWCowboy' or 'WOWCowboy Menthol' tobacco-flavoured cartomizers (18 mg/ml nicotine; commonly used nicotine strength Vapor4Life) were matched to participants' tobacco cigarette flavour preference (i.e. non-menthol or menthol). A new 'cartomizer' and fully charged battery were used for each session. Participants' usual brand of tobacco cigarette was used in the own brand conditions. Device and product: a Categoria e-Cigarettes
Dawkins *et al.*[313] 2013	Benefit	The authors reported on the relationship between nicotine derived from e-cigarettes and time-based prospective memory in abstinent smokers. Age mean years (SD): 31.85 (8.7). Sex: 7 males, 13 females Country: UK. Ethnicity: Caucasian Duration of trial: Two sessions. Conducted on consecutive days. Each testing session lasted approximately 1 hour, outcomes were assessed 15 minutes after each intervention. The trial was conducted over four days, interventions were evaluated on day two and three of the trial Data source: recruited via advertisements, social network forums, e-mail and word of mouth Population size: 20. Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers. All smoked within an hour of waking, smoked more than ten cigarettes a day and had done so for at least 1 year Intervention and research design: This study was employed an open-label, two-sequence, two period, randomized crossover design, that is a within-subjects design was employed; each participant was tested on two occasions after overnight abstinence, with e-cigarette type (nicotine vs. placebo; order counterbalanced) as the independent variable. The two experimental sessions

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		used nicotine (18 mg) and placebo (0 mg) e-cigarette conditions. The placebo condition, therefore, represents the 'abstinent' state. The experimenter introduced the participant to the e-cigarette, explaining and demonstrating how to use it before allowing the participant to use it ad libitum for 10 minutes. Participants were then asked to wait for 15 minutes (to allow time for the nicotine to reach maximum plasma concentration; during which time they completed basic demographic information and the Fagerström Test of Nicotine Dependence (time 1 only). After 15 minutes, participants then completed the Mood and Physical Symptoms Scale and desire-to-smoke scales followed by the Cambridge Prospective Memory Test. Testing at time 2 followed the same procedural format using the parallel version of the Cambridge Prospective Memory Test (order counterbalanced), the demographic questionnaire and the Fagerström Test of Nicotine Dependence were not repeated. At the end of the second session, the participants were debriefed and asked to guess on which occasion they had received nicotine and placebo and then informed accordingly. Each testing session lasted approximately 1 hour. Outcomes: The Cambridge Prospective Memory Test, desire to smoke and tobacco withdrawal symptom specifically measure of depressed, irritable, anxious, drowsy, restless, hungry, unable to concentrate, the calculated outcomes from these measures are Mood and Physical Symptoms Scale (MPSS) total and desire to smoke as assed by the Mood and Physical Symptoms Scale. The authors concluded that compared with placebo, nicotine e-cigarettes reduced the desire to smoke and tobacco withdrawal symptoms, and improved time-based but not event-based prospective memory. There was a moderate, marginally significant negative correlation between prospective memory performance during abstinence and nicotine dependence.[313] Device and product: The 'Tornado' e-cigarette was supplied by Totally Wicked E-Liquid. E-cigarettes were fully charged prior to each assessment session and fitted with either an 18 mg (nicotine) or 0 mg (placebo) cartridge, both of which were tobacco flavoured
Adriaens *et al.*[314] 2014	Benefit	The authors reported on the effectiveness of **e-cigarettes** in an 8-week Flemish study with 6-month follow-up on **smoking reduction, craving, and experienced benefits and complaints**. Age mean years (SD): 43.71 (13.13). Sex: 23 males, 27 females. Country: Belgium Duration of trial: During an eight-week period, participants were asked to come three times (Session 1 in week one, Session 2 in week four, Session 3 in week eight) to a lab session; each session lasted approximately one hour. Three months after the last lab session (FU1), the authors asked all participants to fill out an online questionnaire assessing any changes in terms of smoking or vaping behaviour. Six months after the last lab session (FU2), participants were invited to a follow-up session in which the authors provided some global information about the obtained preliminary results Data source: Participants from the area around Leuven Belgium were recruited through various channels Population size: 51 persons consented to participate, 50 participated and were randomised to one of three groups: E-cigarette 1 n=16, E-cigarette 2 n=17 and Control n=17. At eight weeks laboratory data was available on n=47 (E-cigarette 1 n=15, E-cigarette 2 n=16 Control n=16). At 32-week laboratory data was available on n=36 (cig 1 n=11, E-cigarette 2 n=12 Control n=13) Year of data collection: December 2012 and February 2013 E-cigarette, smoking and other related status: Smokers unwilling to quit smoking

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Intervention and research design: Two different kinds of second-generation e-cigarettes (see below) Outcomes: breath carbon monoxide measurements, saliva samples to determine cotinine levels, craving for cigarettes, withdrawal symptoms, and number of cigarettes per day (assessed via online questionnaires) assessing any changes in terms of smoking or vaping behaviour, Tobacco Craving Questionnaire, the Minnesota Nicotine Withdrawal Scale and a visual analog scale assessing cigarette craving. Complaints and Benefits of cigarette or e-cigarette. E-cigarette Use, Mood The authors concluded that in a series of controlled laboratory sessions with e-cigarette-naive tobacco smokers, second-generation e-cigarettes were shown to be immediately and highly effective in reducing abstinence-induced cigarette craving and withdrawal symptoms, while not resulting in increases in exhaled carbon monoxide. Remarkable (>50%) 8-month reductions in, or complete abstinence from, tobacco smoking was achieved with e-cigarettes in almost half (44%) of the participants.[314] Device and product: Two different kinds of second-generation e-cigarettes, namely the "Joyetech eGo-C" and the "Kanger T2-CC", referred to as respectively type one and type two e-cigarettes. The Joyetech eGo-C consists of a rechargeable 1000 milliampere hour 3.3 V lithium-ion battery, an atomizer body (cover cone and atomizer base) holding a refillable 1 mL cartridge serving as mouthpiece, and a replaceable 2.2-ohm atomizer head. The Kanger T2-CC consists of a replaceable mouthpiece, a 2.4 mL clearomizer, a 2.5-ohm coil and a rechargeable 650 milliampere hour 3.7 V lithium-ion battery. For both types of e-cigarettes the authors used 30 mL bottles of tobacco-flavoured e-liquid (Dekang "Turkish Blend"), containing 18 mg/mL of nicotine. Participants were encouraged to only use this type of e-liquid for reasons of standardization. The e-cigarette groups received the e-cigarette and four bottles of e-liquid at Session 1 (group E-cigarette1 received the Joyetech eGo-C and group E-cigarette2 received the Kanger T2-CC); at Session 2, participants' empty bottles were replenished up to again four bottles and at Session 3, they were allowed to keep the remaining bottles. For these groups, we performed multiple weightings, with a calibrated scale, of the 30 mL bottles containing the e-liquid to derive the average consumption of liquid per day in mL. The control group received the e-cigarette and e-liquid (six bottles) for two months at the end of Session 3 (eight of the 16 participants of the control group received the Joyetech eGo-C and the remaining eight participants received the Kanger T2-CC). All participants received their material for free. All devices and e-liquids for two months were provided by the experimenter
Nides *et al.*[315] 2014	Benefit	The authors reported on the relationship between short-term **smoking reduction with an electronic nicotine delivery system** and **nicotine blood levels, heart rate, and cravings**. Age mean years (range): 43 (18 to 63) baseline assessment. Sex: 66% male. Country USA. Duration of trial: Three sessions. One-week intervals Data source: Subjects were recruited from the study site's database and from the community through advertisements. Population size: 25. Year of data collection: Not reported E-cigarette, smoking and other related status: smoking at least 10 factory-produced cigarette per day for the previous year Intervention and research design: The study consisted of 3 clinic visits at one-week intervals. It was an open-label, noncomparative study. At the end of visit 1, subjects were provided with a diary on which to record the number of

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		conventional tobacco cigarettes they smoked each day over the following week, providing a more accurate baseline measure than the retrospective data collected at visit 1. At visit 2, the diary was returned, and the subjects were instructed on the use of the e-cigarettes, after which they could use the product on an ad libitum basis for 20 minutes while in the clinic. Subjects were given a 10-day supply of the e-cigarettes. This supply was intended to last until visit 3, which was scheduled for 7 days later but could occur up to 10 days later. Depending on preference, subjects received either menthol or nonmentholated e-cigarettes. The subjects were instructed to start using the e-cigarettes on the day after visit 2 and to use them as often as they like (ad libitum) during the following week. No specific instructions on reducing conventional combustible tobacco cigarettes were given. Visit 3 was scheduled for 7 days after visit 2 and data recorded by participant during the study was collect, and pharmacokinetic/pharmacodynamic assessment data were gathered Outcomes: Craving assessment, withdrawal assessment, perception of e-cigarettes, nicotine extraction from product. After 5 minutes of use, blood nicotine levels increased, heart rate increased, and craving was reduced by 55%. Cigarettes per day were reduced by 39% during the test week, and perceptions of use for reduction or cessation were positive. The authors concluded that the NJOY® King Bold e-cigarette delivered nicotine and led to short-term smoking reduction.[315] Device and product: The e-cigarettes used were NJOY® King Bold (NJOY, Inc., Scottsdale, AZ) and were provided to the subjects free of charge by the manufacturer. Externally, these e-cigarettes resemble conventional tobacco cigarettes; but internally, they contain a lithium battery, a surrounded by a cotton wad containing 0.5 mL of nicotine solution These e-cigarettes are neither rechargeable nor refillable; rather, they are disposable. The nicotine solution contains approximately 26 mg of nicotine. The nicotine is dissolved in 2 excipients, namely propylene glycol and glycerol, both present at approximately 40%. The balance of the solution consists of a variety of flavouring agents, each of which is present at less than 0.2% and has received the Flavour Extracts and Manufacturers Association classification as Generally Recognized as Safe for use in food products although their safety in inhaled products has not been confirmed. In addition, one NJOY® King Bold style contained menthol.
Polosa *et al.* [316] 2014b	Benefit	The authors examined the effect of **e-cigarettes as an aid for smokers to quit or reduce cigarette consumption**. The authors concluded that long-term e-cigarette use can substantially decrease cigarette consumption in smokers not willing to quit; in addition, it is well tolerated. Age mean years (SD): 42.3 (±8.6). Sex: 17 males, 6 females Country: Italy. Duration of trial: 24 months Data source: Adult smokers of >=15 cigarettes per day for at least 10 years who were not keen to quit smoking at the time of recruitment or in the forthcoming 30 days, were recruited from the local hospital staff in Catania, Italy. Population size: 40 at baseline 23 completed the study at 24 months Year of data collection: Not reported E-cigarette, smoking and other related status: Adult smokers of >=15 cigarettes per day for at least 10 years who were not keen to quit smoking. Intervention and research design: This study was described by the authors as an observational prospective study following a cohort of smokers in a naturalistic setting after a 24-week intervention phase during which participants were

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		issued with Categoria e-Cigarettes. Specifically, eligible participants were invited to use a 'Categoria' e-Cigarette (Arbi Group Srl, Italy) for a period of 6 months and followed up prospectively for 2 years. After an initial 6-month intervention phase using the e-Cigarette, participants attended two follow-up visits, at 18 and 24 months, at a smoking cessation clinic. As participants were issued with the intervention, Categoria e-Cigarettes, it has been included in the trial category in this review. After an intervention phase of 6 months, during which e-Cigarette use was provided on a regular basis, cigarettes per day and exhaled carbon monoxide (eCO) levels were measured participants were followed up in an observation phase at 18 and 24 months. Outcomes: Efficacy measures included: 50 % reduction in the number of cigarettes per day from baseline, defined as self-reported reduction in the number of cigarettes per day 50 % reduction compared to baseline; 80 % reduction in the number of number of cigarettes from baseline, defined as self-reported reduction in the number of number of cigarettes 80 % reduction compared to baseline; abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking (together with an exhaled carbon monoxide concentration of B10 ppm). Smoking reduction and abstinence rates were computed, and adverse events (throat irritation, mouth irritation, dry cough, dry mouth, dizziness, headache and nausea) reviewed. Of the 40 subjects, 17 were lost to follow-up at 24 months. A 50 % reduction in the number of cigarettes per day at 24 months was shown in 11/40 (27.5 %) participants with a median of 24 cigarettes per day use at baseline decreasing significantly to 4 cig/day (p = 0.003). Smoking abstinence was reported in 5/40 (12.5 %) participants while combined 50 % reduction and smoking abstinence was observed in 16/40 (40 %) participants at 24 months. Five subjects stopped e-Cigarette use (and remined abstinent), three relapsed back to tobacco smoking and four upgraded to more performing products by 24 months. Some mouth irritation, throat irritation, and dry cough were reported. Withdrawal symptoms were uncommon. The authors concluded that long-term e-cigarette use can substantially decrease cigarette consumption in smokers not willing to quit; in addition, it is well tolerated.[316] Device not reported
Polosa *et al.* [319] 2014c	Benefit	The authors reported on success rates with **nicotine personal vaporisers in a prospective 6-month pilot study of smokers not intending to quit**. Age range: 18 to 60 years. Sex: 44 males, 26 females. Country: Italy Duration of trial: 24 weeks Data source: Healthy smokers, smoking ≥15 conventional tobacco cigarettes per day for at least 10 years were recruited using anti-smoking leaflets and by an approved kiosk located in the atrium of the university hospital ('Policlinico-V.Emanuele') promoting smoking cessation services at Centro per la Prevenzione e Cura del Tabagismo, Università di Catania, Italy Population size: 38. Initially, 72 persons were recruited within the hospital setting, 50 subjects were eligible for inclusion in the study at baseline, 38 completed the study at 24 weeks Year of data collection: Not specified E-cigarette, smoking and other related status: Healthy smokers 18 to 60 years old, smoking ≥15 conventional tobacco cigarettes per day for at least 10 years were recruited

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Intervention and research design: as participants were issued with the intervention, it has been included in the trial category in this review. Outcomes: Sustained 50% and 80% reduction in cigarettes per day at week-24 was reported in 15/50 (30%) and 7/50 (14%) participants with a reduction from 25 cigarettes per day to 6 cigarettes per day ($p < 0.001$) and 3 cigarettes per day ($p < 0.001$), respectively. Smoking abstinence (self-reported abstinence from cigarette smoking verified by an exhaled carbon monoxide ≤10 ppm) at week-24 was observed in 18/50 (36%) participants, with 15/18 (83.3%) still using their personal vaporiser at the end of the study. Combined 50% reduction and smoking abstinence was shown in 33/50 (66%) participants. Throat/mouth irritation (35.6%), dry throat/mouth (28.9%), headache (26.7%) and dry cough (22.2%) were frequently reported early in the study but waned substantially by week-24. The authors concluded that the use of second-generation personal vaporisers substantially decreased cigarette consumption without causing significant adverse effects in smokers not intending to quit; in addition, participants' perception and acceptance of the products was very good.[319] Device and product: Participants were given a second-generation personal vaporiser, EGO/CE4 model, and a full supply of tobacco aroma e-Liquid containing 9 mg/ml nicotine for 4 weeks (14 vials in total). Commercially available PV kits (EGO/CE4 model with a rechargeable 3.7 V - 650mAh lithium-ion battery, charger, and CE4 atomizer) and e-Liquids (Tuscan Reserve; FlavourArt –Italy, www.flavourart.it, and Calliope; DEA Flavour – Italy, www.flavourart.it; both consisting of a similar propylene glycol/VG base) were purchased from local vape shops out of a generous grant by LIAF (Lega Italiana Anti Fumo)
Caponnetto *et al.*[317] 2017	Benefit	The authors reported on **cognitive performance, craving, and gesture (physical act of having a conventional combustible tobacco cigarette in hand) in subjects using e-cigarettes and their usual cigarettes**. Age mean years (SD): 34.8 (11.4). Sex: 20 males, 4 females. Country: Italy Duration of trial: Five days. On the first study day, participants were randomized to use one of five different products: first generation rechargeable cigalike, e-cigarettes, loaded with cartridges 24mg nicotine, tobacco aroma; second generation, disposable cigalike e-cigarette loaded with cartridges with 24mg nicotine, tobacco aroma; second generation disposable cigalike e-cigarette loaded with cartridges with 0mg nicotine, mint aroma; second generation electronic, personal vaporizer, model Ego C (tank cartomizer), loaded with liquid nicotine 24 mg, tobacco aroma; with their usual classic cigarettes. Allocation was performed using a random sequence of five codes, each corresponding to one product, prepared in advance by the study statistician using the Latin-square method to control for time effects. Data source: Thirty-four regular smokers were recruited. Population size: 34 Year of data collection: May 2015 to September 2015 E-cigarette, smoking and other related status: Intervention and research design: randomized crossover trial designed to compare cognitive performances, craving, and gesture in subjects who used first generation e-cigarettes, second generation electronic-cigarettes with their usual cigarettes. Craving: in T1,T2,T3,T4,T5,T6. Participants rated their current desire for a cigarette using single item visual analog scale number between 0 and 10, where 0 = "not at all" and 10 ="extremely." Carbon monoxide in exhaled breath (eCO) was measured at T1,T2,T3,T4,T5, T6. Gesture: at minute 2 during the 15 puff. Participants rated their gesture satisfaction for the specific product using a

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		single item visual analog scale number between 0 and 10 (“Right now, how much do you want a cigarette in your hand or in your mouth?”), where 0 = “completely unsatisfying,” 10 = “fully satisfying.” Outcomes: cognitive performances, craving, and gesture in subjects who used first generation e-cigarettes, second generation e-cigarettes with their usual cigarettes The authors concluded that the cognitive measures of attention, executive function, and working memory are not influenced by different e-cigarettes and sex, demonstrating that in general e-cigarettes could become a strong support from a cognitive point of view for those who decide to quit smoking. It seems that not only cravings and other smoking withdrawal symptoms, but also cognitive performance, are linked to the presence of nicotine; this suggests that the reasons behind the dependence and the related difficulty in quitting smoking needs to be examined. The physical act of smoking conventional combustible tobacco cigarettes also needs to be studied.[317] Device and products: first generation rechargeable cigalike, e-cigarette, loaded with cartridges 24mg nicotine, tobacco aroma, second generation, disposable cigalike e-cigarette loaded with cartridges with 24mg nicotine, tobacco aroma, second generation disposable cigalike e-cigarette loaded with cartridges with 0mg nicotine, mint aroma, second generation electronic, personal vaporizer, model Ego C (tank cartomizer), loaded with liquid nicotine 24 mg, tobacco aroma, and usual cigarettes. (a) First generation rechargeable cigalike, e-cigarettes, loaded with cartridges 24mg nicotine (model “401”). The e-Cigarette “Categoria” model “401” was supplied by the manufacturer, Arbi Group Srl (Milano, Italy). It is a three-piece model that closely resembles a tobacco cigarette. Its heating element in the atomizer is activated by a rechargeable 3.7 V–90 milliampere hour lithium-ion battery. A fully charged battery can last up to the equivalent of 50–70 puffs. Disposable cartridges used in this study looked like tobacco cigarette’s filters containing an absorbent material saturated with a liquid solution of propylene glycol and vegetable glycerine in which nicotine or an aroma was dissolved. Disposable cartridges had to fit securely onto the heating element of the atomizer in order to produce a consistent vapor. One type of cartridges was provided for this study day; “Original” 24mg nicotine. Detailed toxicology and nicotine content analyses of these cartridges had been carried in a laboratory certified by the Italian Institute of Health and can be found at: http://www.categoriacigarette.com/. The cartridge labelled “Original 24 mg” contains liquid comprising 1.4% water, 2.37% nicotine, 75.6% propylene glycol, ethanol 0.16, glycerine 19.7%, pyrazine, trimentyl 0.10%, 2,3-dimethylpyrazine 0.13%, myosmine 0.15%. (b) Second generation, disposable cigalike e-cigarette loaded with cartridges with 24mg nicotine, (model 501 “ONE original”). This is a single use electronic cigarette. Compared to “Categoria” E-cigarette (model “501”), the model ONE high original has a new filter technology that comprises an integrated atomizer and a new long-life battery, which guarantee high performance. Externally, these electronic cigarettes resemble conventional tobacco cigarettes; but internally, they contain a lithium battery, a heater unit, an integrated circuit, and a wick surrounded by a cotton wad containing 0.5 mL of nicotine solution. These electronic cigarettes are neither rechargeable nor refillable; rather, they are disposable. The nicotine solution contains approximately 24mg of nicotine. Detailed toxicology and nicotine content analyses of these cartridges had been carried in a laboratory certified by the Italian Institute of Health and can be found at: http://www.categoriacigarette.com/it/studi-e-ricerche/analisi/analisi-2013. The cartridge contains liquid comprising 2.2% Nicotine, 21.2% Glycerine,

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		70.8% Propylene Glicol, <0.1% Ethylene Glicol, 4.5% Water, 0.4% Flavors and Additives, <5% Cadmium l, <5% Lead, <1% Mercury, <5% Chromium. (c) Second generation disposable cigalike e-cigarette loaded with cartridges with 0mg nicotine, mint aroma (model 501 "ONEMint"). This is a single use e-cigarette. Compared to "Categoria" E-cigarette (model "501"), the model ONE Mint has a new filter technology that comprises an integrated atomizer and a new long-life battery, which guarantee high performance. Externally, these electronic cigarettes resemble conventional tobacco cigarettes; but internally, they contain a lithium battery, a heater unit, an integrated circuit, and a wick surrounded by a cotton wad containing 0.5 mL of nicotine solution. These e-cigarettes are neither rechargeable nor refillable; rather, they are disposable. Detailed toxicology and nicotine content analyses of these cartridges had been carried in a laboratory certified by the Italian Institute of Health and can be found at: http://www.categoriacigarette.com/it/studi-e-ricerche/analisi/analisi-2013. The cartridge contains liquid comprising <0.001% Nicotine, 18.8% Glycerine, 72.5% Propylene Glicol, 2.1% Ethylene Glicol, 4.9% Water, 0.78% Flavors and Additives, <5% Cadmium l, <5% Lead, <1% Mercury, <5% Chromium. (d) Second generation electronic, personal vaporizer, model Ego C (tank cartomizer), loaded with liquid nicotine 24 mg, tobacco aroma. The e-cigarette ("Ego") were supplied by, Fumo digitale (Varese,Italy). The e-cigarette Ego C (Joyetech), used in the study, consist of the atomizer, the tank cartomizers and the battery. This e-cigarette is considered—second generation; the battery has higher capacity compared to cigarettelike devices and the atomizer design is different compared to polyfil-containing cartomizers. A 24 mg/ml nicotine-containing liquid was used (Tuscan flavor by Flavouart), which is generally considered high strength. The E-liquid Tuscan by Flavourart were supplied by Flavourart (Oleggio-NO, Italy). This E-liquid comprising 0.80 g USP Nicotine, 44.82 g USP Glycerine, Propylene Glicol USP 46.7 g, 8.11 gWater, <0.5 g Flavors.(e) Participants usual classic cigarettes.
Hiler *et al.*[335] 2017	Harm	The authors looked at the relationship between nicotine delivery profile and cardiovascular and subjective effects. Age mean years (SD): 30.6 (9.1). Sex: Not reported. Country USA Duration of trial: Four sessions. Intervention 48 hours. Eight days. Participants completed four, double-blind ~2.5-hour sessions at the Clinical Behavioral Pharmacology Laboratory. Session order was randomized and sessions were separated by a minimum of 48 hours Data source: community volunteers were recruited by advertisement and word of mouth Population size: 64. Year of data collection: Not reported E-cigarette, smoking and other related status: E-cigarette-experienced individuals and e-cigarette-naïve cigarette smokers Intervention and research design: Four double-blinded ~2.5hour sessions. Session order was randomized and sessions were separated by a minimum of 48 hours. Outcomes: Plasma nicotine and heart rate, Puff topography, subjective questionnaires including the modified Hughes-Hatsukami on withdrawal scale, the Direct Effects of e-cigarette-use scale which assesses the extent to which the topography mouthpiece interfered with normal e-cigarette-use behaviour and the Tiffany-Drobes Questionnaire of Smoking Urges Brief The authors concluded that participants' plasma nicotine concentration was related directly to liquid nicotine concentration and was dependent on user experience, with significantly higher mean plasma nicotine increases observed

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		in e-cigarette-experienced individuals relative to e-cigarette-naive smokers in each active nicotine condition.[335] Device and products: Thirty-three e-cigarette-experienced individuals and 31 e-cigarette-naïve cigarette smokers completed four laboratory conditions that consisted of two, 10-puff bouts (30-second IPI) with a 3.3-volt e-cigarette battery attached to a 1.5 Ohm "cartomizer" (7.3 watts) filled with 1 ml e-cigarette liquid. Conditions differed by liquid nicotine concentration: 0, 8, 18, or 36 mg/ml
Stiles *et al.*[331] 2017	Beneficial, but less beneficial than tobacco cigarettes	The authors evaluated the **abuse liability of three Vuse Solo e-cigarettes** with a nicotine content ranging from 14 mg cartridge, to 29mg, and to 36 mg, relative to high- and low-abuse liability comparator products (usual brand combustible cigarettes and nicotine gum, respectively). Age mean years (SD): 39.7 ± 11.15. Sex: 34 males, 25 females Country: USA. Ethnicity: Asian (1) White (56) White, American Indian/Alaska Native (2) Duration of trial: Five test visits. 35 days. Outcomes were gathered up to six hours after the clinic intervention was undertaken. Prior to each visit subject the investigational product was 'home used' for 7 days. Product use during the ambulatory periods was non-exclusive, subjects were allowed to smoke their usual brand cigarettes throughout the study. In clinic product use, all ad libitum, consisted of up to 10 minutes use of Vuse Solo or smoking of one cigarette, or up to 30 minutes using nicotine gum according to the package instructions (i.e., 'park and chew' method). A series of timed blood samples was collected for measurement of nicotine concentration to assess uptake from product. Collection times were up to 360 minutes relative to the subject starting use of product. Data source: Not reported Population size: One hundred twenty-one subjects took part in the screening procedures, 59 subjects were randomized, and 45 subjects completed all five test visits. Fourteen subjects were withdrawn from the study, including one subject who was discontinued due to adverse events (judged to be unrelated to study product), eight subjects who were discontinued due to protocol deviations, and five subjects who withdrew consent for study participation. Year of data collection: Not reported E-cigarette, smoking and other related status: Electronic-naive smokers. Subjects were required to smoke 10 or more non-menthol 83 mm (king size) to 100 mm combustible filtered cigarettes per day for at least 6 months, and typically smoke their first cigarette of the day within 30 minutes of waking. Characteristics of the study population showed: cigarettes per day mean (SD) 20.6 (6.34) Fagerström Test for Nicotine Dependence score Mean SD 5.8 (1.29). A total of 30 different usual brand cigarette brand styles were reported as currently being smoked at the time of screening. Nearly half of the subjects reported smoking the four most common usual brand cigarette styles: Marlboro Red (n = 8, 14%), Marlboro Gold (n = 8, 14%), Pall Mall Red (n = 6, 10%), and Camel Blue (n = 5, 9%). Other brand styles were smoked by four or fewer (≤7%) subjects each. No subject reported regular use of electronic-cigarettes prior to entering the study. Intervention and research design: Five clinic visits. Crossover. Eligible subjects who successfully passed all screening requirements were enrolled into the study and randomized to a product use sequence. A 7-day ambulatory (home use) trial of each investigational product (including a week of using only usual brand cigarette) preceded each of five test visits to allow subjects to become

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		accustomed to using the new products. Product use during the ambulatory periods was non-exclusive, as subjects could smoke their usual brand cigarettes throughout the study. Product use was tracked daily using an electronic diary, with subjects documenting the number of usual brand cigarettes smoked and the number of 'uses' of Vuse Solo or nicotine gum per day (data not presented). One 'use' of Vuse Solo or nicotine gum was defined as approximately 10 to 30 minutes of ad libitum use, respectively, to approximate use in test visits. Subjects were instructed to use the assigned investigational product at least once per day for 6 of the 7 days prior to each test visit; subjects were not to use the dispensed investigational products on the day immediately prior to the test visit. Subjects were to abstain from all tobacco and nicotine products for at least 12 h prior to each test visit to minimize the impact that residual nicotine concentrations might have on baseline subjective and physiological measurements. Subjects reported to the clinic on the morning of each test visit and were initially assessed for continued eligibility and compliance with the required 12-h smoking abstention. Subjects with an expired carbon monoxide value >12 ppm were not eligible to participate in the clinical procedures on that day but were allowed to reschedule one test visit for this reason. In clinic product use, all ad libitum, consisted of up to 10 minutes use of Vuse Solo or smoking of one cigarette, or up to 30 minutes using nicotine gum according to the package instructions (i.e., 'park and chew' method). Serial blood sampling, questionnaires, and physiological measurements were completed at the specified time points relative to the start of product use. Individual Vuse Solo cartridge weights, before (initial weight) and after (final weight) in-clinic use, were recorded to assess the amount of product use. In-clinic use of each of the three types of products occurred in separate sections of the clinic to minimize any potential effects of environmental aerosol or tobacco smoke or other sensory cues on subjective effects assessments. Subjects underwent End-of-Study procedures at test visit 5 (or early termination), including a symptom-driven physical examination, a brief oral examination, and collection of blood and urine samples for clinical laboratory tests. Outcomes: Physiological measures included pulse rate, systolic and diastolic blood pressure, and expired carbon monoxide. Baseline cotinine concentrations were also measured to assess whether subjects substantially changed their nicotine uptake during the study. Safety and tolerability were evaluated based on data collected from physical and oral examinations, clinical laboratory tests, vital sign measurements, electrocardiograms, and adverse events. Enrolled subjects' ratings of subjective effects and nicotine uptake over 6 h were used to measure abuse liability and pharmacokinetics following in-clinic use of each electronic cigarette. The authors concluded that the use of Vuse Solo e-cigarettes resulted in subjective measures (product liking, intent to use product again, product effects, urge to smoke, and urge for product) and nicotine uptake that were between those of combustible cigarettes and nicotine gum, although generally closer to nicotine gum. Compared with combustible cigarettes, use of Vuse Solo e-cigarettes resulted in significantly lower scores in measures of product liking, positive effects, and intent to use again. These pharmacodynamic findings were consistent with the pharmacokinetic data, showing that tobacco cigarettes produced substantially faster and higher levels of nicotine uptake when compared with Vuse Solo e-cigarettes and nicotine gum. Vuse Solo e-cigarettes resulted in more rapid initial uptake of nicotine compared to nicotine gum, but peak concentration and long-term extent of uptake were not different or were lower with Vuse Solo e-cigarettes. Collectively, these findings suggest that Vuse Solo cigarettes likely have an abuse liability that is somewhat greater than nicotine gum but lower than cigarettes).[331]

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Device and product: Three, non-menthol, commercially available brand styles of Vuse Solo were evaluated in this study, containing either 14, 29, or 36 mg of nicotine. Vuse Solo ECs are composed of a battery, heating element, microchips, sensor, and a cartridge containing propylene glycol, glycerin, nicotine, flavourings, and water. The three electronic-cigarettes were presented without brand style information and were visually indistinguishable by subjects. Cigarettes: Usual brand cigarettes (any combustible, filtered, nonmenthol brand style, 83 mm [king size] to 100 mm in length) and Nicorette® White Ice Mint nicotine polacrilex gum, 4 mg (GlaxoSmithKline Consumer Healthcare, L.P.) were chosen as high and low abuse liability comparator products, respectively, to assess the relative abuse liability of Vuse Solo. The three Vuse Solo ECs and nicotine gum were provided at no cost to subjects, while subjects provided their own usual brand cigarettes throughout the study.
Adriaens *et al*.[1] 2018	No benefit	Authors reported on a three-day randomized crossover trial, focusing on the **behavioural and experiential effects of the short-term use of the heat-not-burn product IQOS™**, versus an e-cigarette, and versus a regular cigarette, in current smokers who were novice users for both IQOS™ and e-cigarettes. To investigate the effect of using an IQOS™ on exhaled carbon monoxide, **acute cigarette craving, withdrawal symptoms, and subjective positive and negative experiences** after overnight smoking abstinence, compared to using an e-cigarette or a regular tobacco cigarette. And to investigate which product (e-cigarette or IQOS™) would be preferred. Age mean years (SD): 22 (3.09). Sex: 67% males Country: Belgium. Ethnicity: Belgian nationality (47%) with the remaining being of other nationalities (e.g., Italian, Pakistani, Indian, etc.) Duration of trial: Three sessions. Three consecutive days after being overnight smoking abstinent. During each session, participants used one of three products (cigarette, e-cigarette, or IQOSTM) for five minutes. Exhaled CO (eCO) measurements and questionnaires were repeatedly administered throughout the session Data source: Dutch and English-speaking participants via various channels around the University of Leuven (i.e., distribution of flyers in University buildings and local newspaper shops, social media). Population size: 30. Year of data collection: Not reported E-cigarette, smoking and other related status: Regarding smoking history, participants started smoking on average at the age of 16 (SD = 1.84) and started smoking regularly at the age of 18 (SD = 1.77). One-third had tried (M = 2.00 times, SD = 0.94) to quit smoking in the past, mainly using willpower (90%). The longest quit-smoking period (with all using willpower) had lasted on average five months (SD = 9.02), with a minimum of one month and a maximum of 30 months. Intervention and research design: Randomized, crossover behavioral trial. It was a crossover, counterbalanced, within-subjects design for the laboratory sessions. Participants came to the lab (individually or in group, with a maximum of three participants) on three consecutive days, each time at the same hour of the day; each session lasted 70 to 80 minutes and followed the same procedure. Next, participants could use one of the three products ad lib for five minutes outside the building (only one cigarette or heat-stick were allowed). In each session, only one product was used and the order of product use over the days was completely counterbalanced between participants to control for order effects. Finally, at fixed moments (T1, T2, T3, T4, and T5) participants filled out questionnaires and performed exhaled carbon monoxide measurements. At the

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		end of the session, the authors scheduled the three laboratory sessions with each participant. They used a crossover, counterbalanced, within-subjects design for the laboratory sessions. Participants came to the lab (individually or in group, with a maximum of three participants) on three consecutive days, each time at the same hour of the day; each session lasted 70 to 80 minutes and followed the same procedure. Before each laboratory session, participants needed to abstain from smoking for 12 h. At the start of the session (T0), participants filled out questionnaires and performed an exhaled carbon monoxide-measurement. In the corresponding session, participants received a brief rehearsal on how to use the e-cigarette or IQOSTM. Next, participants could use one of the three products ad lib for five minutes outside the building (only one cigarette or heat-stick were allowed). In each session, only one product was used and the order of product use over the days was completely counterbalanced between participants to control for order effects. Finally, at fixed moments (T1, T2, T3, T4, and T5;) participants filled out questionnaires and performed exhaled carbon monoxide measurements Outcomes: Changes in exhaled carbon monoxide levels, changes in cigarette craving throughout the sessions, withdrawal symptoms measured MNWS-R, product evaluation and preferences The authors concluded that short-term use of a specific heat-not-burn product, IQOSTM, can be effective to momentarily reduce acute cigarette craving and withdrawal symptoms, while having a minimal impact on the exhaled carbon monoxide levels, and being slightly more liked by novice users than an e-cigarette. They stated however that this does not guarantee that craving/withdrawal symptom reduction will also be sustained over longer time spans or in case of repeated use, nor do they provide assurance that these effects are sufficient to lead to smoking reduction or cessation in smokers willing to quit or cut down on cigarettes.[1] Device and product: Three products were used during the laboratory sessions—a regular tobacco cigarette, an e-cigarette and the IQOSTM HnB tobacco product. Specifically, they were an Eleaf iStick Power 5000 milliampere hour battery, fixed at 8 W, with an Aspire Nautilus 2 tank containing a 1.6 Ohm coil. The e-liquid ("Base Aurora") contained 18 mg/mL nicotine, a PG/VG ratio of 70/30, to which either a tobacco flavour ("7 Leaves", 3 vol%) or a menthol flavour ("Mild Winter-Peppermint", 3 vol%) was added. Both base liquid and flavours were purchased online (https://www.clubderdampfer.de and https://flavourart.com, respectively).
Baldassarri *et al.*[326] 2018	Harm	The authors examined the relationship between **e-cigarette use and Beta2*-nicotinic acetylcholine receptors** (β2*-nAChR) occupancy. Age mean years (SD): 26 ± 4. Sex: 6 males, 1 female. Country: USA Duration of trial: Two to three sessions with at least 2 weeks between sessions. Six weeks duration. Participants had between two or three scan sessions where e-cigarette users (8 mg/ml and 36 mg/ml, or 0, 8 and 36 mg/ml exposures n=2 for each group) and one session where tobacco cigarette users only. The time period used to quantify occupancy was 180 to 210 minutes (55 to 85 minutes post challenge). Post-nicotine scanning continued until the end of 210 minutes of infusion. Measures were collected during and up to 210 minutes post intervention Data source: Not reported. Population size: 7. Year of data collection: Not specified E-cigarette, smoking and other related status: Four experienced e-cigarette users and 3 cigarette smokers participated in the study

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Intervention and research design: Before and after nicotine challenge with 0, 8, and 36 mg/ml nicotine in a 3.3 Volt, 1.5 Ohm EC or a standard tobacco cigarette Outcomes: β2*-nAChR occupancy by nicotine, arterial blood plasma nicotine levels and liking and craving ratings. Average β2*-nAChR occupancy was higher after 36 mg/ml EC challenge compared to 8 mg/ ml EC at trend level. Average β2*-nAChR occupancy after tobacco cigarette smoking was 68 ± 18% and was not different compared with 8 mg/ml (64 ± 17%,) or 36 mg/ml (84 ± 3%) nicotine in EC users. Area under the curve of blood nicotine level was higher in the cigarette smoking group compared with the 8mg/ml group (p = 0.03), but similar compared with the 36 mg/ml EC (p = 0.29). Drug craving was reduced after use of the tobacco cigarette, 8 mg/ml EC, and 36 mg/ml EC The authors concluded that the e-cigarettes studied have abuse liability and may provide an adequate alternative nicotine delivery system for cigarette smokers.[326] Device and product: e-Go type EC battery (3.3 V, 1000 milliampere hour) with 1.5 ohm dual-coil 510-style cartomizer and a 70/30 propylene glycol/vegetable glycerine e-liquid ("tobacco flavour") with nicotine concentration of 0 mg/ml (n = 2), 8 mg/ml (n = 4) and 36 mg/ml (n = 4). E-liquid nicotine concentrations were measured with a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS) method with a linear range of 0.5 to 50 mcg/mL. Initially, a 0.050 mL aliquot of each liquid was diluted 1000-fold in acetonitrile, along with the addition of a stable isotopically labelled internal standard (nicotined4). This sample was further processed and injected (0.010 mL) into the LC-MS for quantitative analysis.
Hobkirk *et al.*[332] 2018	Harm	The authors reported on **changes in resting state functional brain connectivity and withdrawal symptoms associated with acute e-cigarette use.** Age range: 25 to 58 years. Sex: Not reported. Country: USA Duration of trial: One session. Measures were gathered during and shortly after intervention Data source: Participants were recruited from an online anonymous survey posted on websites and e-cigarette forums Population size: 9. Year of data collection: Not reported E-cigarette, smoking and other related status: Participants using an e-cigarette for at least 20 days out of the last 28 with a nicotine concentration in their e-cigarette liquid of at least 12 mg/mL. Intervention and research design: Participants completed a before and after resting state functional brain connectivity. The before session was undertaken after 14 hours of nicotine abstinence and the after session followed an episode with their own e-cigarette device. Outcomes: Resting state functional brain connectivity (rsFC) The authors concluded that the preliminary results suggest that the effects of e-cigarette use on resting state functional brain connectivity are like those seen with nicotine administration in other forms.[332] Device and product: All participants reported having a preferred device, but only 5 had a preferred liquid flavour; 8 out of 9 participants used a device larger than a combustible cigarette that included a manual button to initiate heating of the coil prior to puffing. Devices cost between $15 and $160 dollars (M=52.33; SD=43.10) and participants reported spending between $3 and $15 dollars per week to maintain their device. The strength of nicotine concentration in liquids ranged from 12 to 24 mg/mL (M=16.44; SD=4.22).

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
Ruther *et al.*[327] 2018	Harm, but less than tobacco cigarettes	The authors reported on the **nicotine delivery efficiency of first- and second-generation e-cigarettes** and their impact on relief of cravings during the acute phase of use. Age mean years (SD): 28.5 ± 8.9 e-cigarette group, 26.2 ± 6.9 tobacco cigarette group Sex: All males. Country: Germany Duration of trial: Four study visits at one-week intervals. Measures were gathered during intervention. Data source: Volunteers were recruited for participation in the study via flyers and over the Internet. Population size: 20. Year of data collection: Not reported. E-cigarette, smoking and other related status: e-cigarette group (n =9) the tobacco cigarette group (n = 11) Participants in the e-cigarette group had been routine users of nicotine-containing e-cigarettes (so-called vapers) for over 3 months and had not smoked a tobacco cigarette for more than one month. None of the vapers had previously used a disposable e-cigarette, i.e. a cigalike. Participants in the tobacco cigarette group had been smoking tobacco cigarettes for at least 3 years and smoked at least 5 cigarettes a day. Intervention and research design: The participants in the e-cigarette group attended four study visits at one-week intervals. At each visit, they used a different kind of e-cigarette in a non-randomized open design crossover Outcomes: Blood nicotine levels during the acute phase in people using first- and second-generation e-cigarettes were monitored and compared with blood nicotine levels in people using a tobacco cigarette. Heart rate changes were measured, and withdrawal symptoms and craving were assessed with the German version of the Questionnaire on Smoking Urges (QSU-G) before and immediately after the vaping/smoking sessions. After five minutes of e-cigarette or tobacco cigarette use, the mean nicotine plasma concentrations were as follows: disposable cigalikes,5.5 ng/ml; tank model, 9.3 ng/ml; tobacco cigarette, 17.1 ng/ml. Nicotine levels increased significantly faster in the first 4 minutes of consuming a tobacco cigarette than with the disposable cigalikes and the tank mode. The highest rate of increase in nicotine concentration was found with the tobacco cigarette (6.8 ng/ml) and tank model (2.3 ng/ml) between the 1st and 2nd minute, whereas the disposable cigalikes showed comparatively small changes in the amount delivered over the five minutes. Withdrawal and craving for smoking decreased with the tank mode by the same amount as with the tobacco cigarette, even though less nicotine was delivered to the blood and considerably fewer side effects occurred. The authors concluded that the heart rate of tank mode users was markedly lower than that of the tobacco cigarette users. Unlike disposable cigalikes, tank mode e-cigarettes represent an effective source of nicotine and might be used as an alternative nicotine replacement product to aid smoking cessation. However, nicotine plasma levels observed in tank mode users after short-term vaping also have the potential to produce and sustain nicotine addiction.[327] Device and product: Cigalikes: Name (Manufacturer and Nicotine content (mg/ml) according to manufacturer): American Heritage (American Heritage International (18.0 mg/ml) Vype (British American Tobacco (18.6 mg/ml)) Blu (Imperial Brands (18.0 mg/ml)) Tank model: Aspire/Joyetech Upgrade Seta (Hybrid technology with Aspire Maxi BDC clearomizer and Joyetech eGo-C 2 upgrade battery (Aspire/Joyetech (18.0 mg/ml))

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Tobacco cigar: Marlboro Red (Philip Morris International (0.8 mg/cigarette mg/ml)
Cobb *et al.*[328] 2019	Harm	The authors reported on the **influence of e-cigarette liquid flavours and nicotine concentration on subjective measures of abuse liability** in young adult e-cigarette vapers. Age mean years (SD): 19.9 (1.1) . Sex: 10 males, 10 females. Country USA Ethnicity: 40% White Non-Hispanic, 35% Black Non-Hispanic, 25% Other Data source: Not reported Population size: 20. Year of data collection: Not reported E-cigarette, smoking and other related status: Smoking at least five cigarettes per day for the past three months Outcomes: Heart rate/blood pressure indicated nicotine exposure during nicotine-containing conditions. Own brand and tobacco/menthol 36 mg/ml conditions produced significant decreases in ratings of cigarette smoking urges. Nicotine/drug effects were elevated significantly for own brand and 36 mg/ml e-cigarette conditions with one exception noted for the tobacco/menthol 0 mg/ml condition. Own brand had the highest acceptability ratings, and e-cigarette condition results varied by acceptability item. Intervention and research design: seven Latin-square order conditions differing by the product used: own brand cigarette or e-cigarette cartomizer loaded with 1 ml of one of three liquid flavors (Food/ Dessert/Spice, Fruit, or Tobacco/Menthol at either 0 or 36 mg/ml nicotine concentration. The authors concluded that among young adult vapers, e-cigarette containing nicotine were positively associated with several, but not all, subjective measures of abuse liability. Flavours did not consistently mask/enhance the effects observed. The results reinforce continued examination of e-cigarette-delivered nicotine and liquid flavours in relation to abuse liability.[328] Device and product: Participant's self-reported own brand cigarettes were purchased locally following enrolment. For all e-cigarette conditions, the e-cigarette device and cartomizer used was an eGo 3.3–4.1 V, 1100 mA h battery and a 1.5- Ohm, dual-coil, 510-style cartomizer. E-CIGARETTE liquid nicotine concentration was verified by the VCU Bioanalytical Core Laboratory (levels were either below the level of quantification for 0 mg/ml or within 2 mg/ml for 36 mg/ml). All e-cigarette liquids were labelled as 70% propylene glycol/30% vegetable glycerine. To determine the specific e-cigarette liquid flavours within the Food/Dessert/Spice and Fruit flavour categories, a content analysis of preferred e-cigarette liquid flavours among adult e-cigarette users (age 18+ and used an e-cigarette for at least 1 month) Four unique liquid flavours at the solvent and nicotine concentration ratios specified above were sourced from a local e-cigarette vendor (AVAIL Vapor, LLC, Richmond, VA): Food/Dessert/Spice (Cream), Fruit (Tropical Fruit), Tobacco, and Menthol. Participants were matched to their own brand menthol preference.
De La Garza *et al.*[321] 2019	Harm	The authors reported on **e-cigarette-naive cigarette smokers and the effects on cravings** after acute exposure to e-cigarettes in the laboratory. Age mean years (SD): 50.6 (7.6). Sex: 10 males, 5 females. Country: USA Duration of trial: Four sessions. Interval of 7 days. Data source: Participants were recruited to the study from the Houston area via newspaper, internet advertisements, flyers, and referral Population size: 15. Year of data collection: Not reported

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		E-cigarette, smoking and other related status: Participants consisted of non-treatment seeking combustible cigarette smokers who reported having never tried an e-cigarette Outcomes: Assessments of craving and smoking severity Intervention and research design: A within-subjects, placebo-controlled study design, 15 tobacco-dependent, e-cigarette naïve participants sustained abstinence overnight. They completed distinct phases of this protocol during four separate study sessions. Participants were randomized to an e-cigarette device containing one of three doses of nicotine (0, 18, or 36 mg/ml) or their own cigarette. Each study visit was ~3 hours long and separated by at least 7 days. Participants completed four distinct sessions separated by at least 7 days The authors concluded that e-cigarettes did not reduce cravings or smoking severity in e-cigarette-naive smokers.[321] Device and product: The combustible cigarettes used in this pilot study were the participants' own brand. The e-cigarettes used were eGo devices with a 3.3-V e-cigarette battery attached to a 1.5-ohm dual-coil cartomizer (Smoktech, Shenzhen, China). The study's e-liquid was Virginia Pure tobacco flavored, containing 0, 18, or 36 mg/ml nicotine loaded with 1ml of a 70% propylene glycol/30% vegetable glycerin (Avail Liquids, Richmond, VA). Nicotine levels were independently assessed and confirmed. The 18 and 36 mg doses were chosen based on the Lopez study, which demonstrated that these were the only doses resulting in a reliable increase in nicotine plasma concentrations
Hughes *et al.*[324] 2019a	Both benefit and harm	The authors reported on the **symptoms of nicotine withdrawal in former smokers who were current daily e-cigarette users.** Age mean years (SD): 31 (10). Sex: 80% males. Country: USA Duration of trial: Two weeks. Three days per week. Data source: Not reported Population size: 109. Year of data collection: Not reported E-cigarette, smoking and other related status: Former smokers who were current daily e-cigarette (e-cigarette) users Outcomes: Symptoms of nicotine withdrawal daily via an Interactive Voice Response system Intervention and research design: Unblinded, within-participants, pre–post clinical trial in which 109 former smokers who were current daily e-cigarette (e-cigarette) users used their own e-cigarette for 7 days followed by 6 days of biologically confirmed abstinence engendered via an escalating contingency payment system The authors concluded that former smokers who are daily e-cigarette users transfer physical dependence on tobacco cigarettes to dependence on e-cigarettes. The severity of withdrawal from e-cigarettes appears to be only somewhat less than that from daily tobacco cigarette use.[324] Device and product: second-generation products with high nicotine levels
Hughes *et al.*[329] 2019c	Harm	The authors reported on **withdrawal symptoms from e-cigarette abstinence among adult never-smokers.** Age mean years (SD): 22 (4). Sex: 60% male. Country: USA Duration of trial: Two week. Assessments made in three days in the second week. Data source: Not clear. Population size: 30. Year of data collection: Not reported

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		E-cigarette, smoking and other related status: Never-smokers, defined as those who used < 100 cigarettes in their lifetime and had no current "regular use" of other nicotine/tobacco products other than current e-cigarette use. Participants also had to currently use refillable nicotine containing e-cigarettes daily and currently use no other nicotine or tobacco products. Outcomes: Withdrawal symptoms measured using the Mood and Physical Symptoms Scale Intervention and research design: Un-blinded pre-post clinical trial The authors concluded that withdrawal symptoms can occur in never-smokers who are daily e-cigarette users. However, the severity of withdrawal from e-cigarette abstinence in never-smokers appears to be small and may not be of clinical or regulatory significance.[329] Device and product: See above
Maloney *et al.*[325] 2019	More harmful than NRT. Harm, but less harmful than tobacco cigarettes	The authors conducted an **abuse liability assessment of an e-cigarette use in combustible cigarette smokers.** Ethnicity: Non-Hispanic White or Caucasian n=6, Non-Hispanic Black or African American Age mean years (SD): 30.9 (9.5). Sex: 18 males, 6 females. Country USA. Duration of trial: Four separate lab sessions that were separated by a minimum of 48 hr. Each four sessions were each approximately 5 hr long. Eight days. Data source: The sample was limited to e-cig-naïve smokers to ensure that the positive control (own brand cigarettes) would test unequivocally positive Population size: 24. Year of data collection: Not reported E-cigarette, smoking and other related status: e-cig-naïve smokers Intervention and research design: Once screening was complete, eligible participants were scheduled for four separate lab sessions that were separated by a minimum of 48 hours. In each session, participants used one of four study products: own brand cigarettes, e-cigarettes with nicotine (e-cig_36), e-cigarette without nicotine (e-cig_0), and IN. These four sessions were each approximately 5 hours long, Latin square ordered, and e-cigarette conditions were double-blind (keeping participants and staff blind to the cigarette and the inhaler conditions was not feasible). Outcomes: The Multiple-choice procedure a pen-and-paper task that measures and allows for comparisons of abuse liability between different drugs and drug delivery platforms, by choosing between increasing amounts of money or 10 puffs from the study product used in that session. Physiological measures for plasma nicotine concentration, monitored heart rate (every 20 s) and blood pressure (every 4 minutes), expired CO. Specifically: Multiple-choice procedure, Plasma nicotine, heartbeat, Systolic BP, Diastolic BP, Subjective measures: Hughes and Hatsukami Tobacco Withdrawal Scale, Anxious, Craving, Depression, Difficulty concentrating, Drowsy, Hunger, Impatient, Irritable, Restless, Sweats, Urge Direct effects of nicotine: Confused, Dizzy, Headache, Heart pound, Light-headed, Nausea, Nervous, Salivate, Sweaty, Weak, Direct effects of product: Awake, Calm, Concentrate, Dizzy, Pleasant, Reduced hunger, Right now, Satisfy, Sick, Taste good. Tiffany–Drobes: Factor 1, Factor 2 The authors concluded that the abuse liability of the e-cigarette examined was higher than the Food and Drug Administration-approved nicotine inhaler but lower than combustible cigarettes.[325]

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		Device and products: e-cigarette (1.5 Ohm, 3.3 V) filled with 36 mg/mL or 0 mg/mL nicotine to a Food and Drug Administration-approved nicotine inhaler and participants' own brand of cigarettes.
O'Connell *et al.*[318] 2019	Both benefit and harm	The authors evaluated the **pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations** in adult smokers in the USA. Age mean years (SD) (range): 42.3 ± 12.41 (24 to 62). Sex: 9 males, 6 females Country: USA Duration of trial: Six sessions. Six days. Plasma nicotine pharmacokinetic assessment was the primary outcome measure for this study. On each study day (Days 1–6), 4 mL of whole blood was collected 5 minutes prior to and at 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, and 30 minutes following the start of product use. Data source: Population size: 15. Year of data collection: Not reported E-cigarette, smoking and other related status: Healthy American smokers. Smoking characteristics 10 'full flavour' cigarettes; 5 'light' cigarettes, 1 menthol, 14 non-menthol The five e-cigarette products tested were (1) myblu pod-system containing 25-mg nicotine ('freebase') tobacco flavour; (2) myblu pod-system containing 16-mg nicotine lactate tobacco flavour; (3) myblu pod-system containing 25-mg nicotine lactate tobacco flavour; (4) myblu pod-system containing 40-mg nicotine lactate tobacco flavour; and (5) blu PRO open system containing 48-mg nicotine lactate tobacco flavour. The reference cigarettes, provided by the subjects, were their preferred brand of commercially available conventional cigarette. Outcomes: Pharmacokinetic profiles and subjective effects of nicotine from two e-cigarette device platforms with varying concentrations of nicotine lactate (nicotine salt) e-liquid relative to conventional tobacco cigarettes The authors concluded that the rate of nicotine absorption into the bloodstream was comparable among all e-cigarettes tested and was as rapid as that for conventional combustible tobacco cigarettes. However, in all cases, nicotine delivery did not exceed that of the conventional combustible tobacco cigarette. The pharmacokinetic profiles of nicotine salt emissions were also dependent upon the properties of the e-cigarette device. Subjective scores were numerically highest after smoking a conventional combustible tobacco cigarette, followed by the Myblu 40 mg nicotine salt formulation per cigarette. The rise in nicotine blood levels following use of all tested e-cigarettes was quantified as 'a little' to 'modestly' satisfying in terms of relieving the desire to smoke. All products were well tolerated with no notable adverse events reported. These results demonstrate that, while delivering less nicotine than a conventional combustible tobacco cigarette, the use of nicotine salts in e-cigarettes enables cigarette-like pulmonary delivery of nicotine that reduces the desire to smoke.[318] Device and product: The five e-cigarette products tested were (1) myblu pod-system containing 25-mg nicotine ('freebase') tobacco flavour; (2) myblu pod-system containing 16-mg nicotine lactate tobacco flavour; (3) myblu pod-system containing 25-mg nicotine lactate tobacco flavour; (4) myblu pod-system containing 40-mg nicotine lactate tobacco flavour; and (5) blu PRO open system containing 48-mg nicotine lactate tobacco flavour. The reference cigarettes, provided by the subjects, were their preferred The myblu device is a rechargeable, closed pod-system e-cigarette, consisting of two segments. A rechargeable battery section (battery capacity, 350 milliampere hour) and a replaceable e-liquid containing pod (volume, 1.5 mL; coil resistance, 1.3 ohm). The myblu device delivers on average 7–8 mg of

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		aerosol per puff under machine vaping conditions. The blu PRO device is a rechargeable, open-system e-cigarette, consisting of two segments. A rechargeable battery section (battery capacity, 1100 milliampere hour) and a refillable clearomiser (volume, 2.0 mL; coil resistance, 1.8 ohm). The blu PRO device delivers on average 2–3 mg of aerosol per puff
Solingapuram Sai *et al*[333]. 2019	Both benefit and harm	The authors reported on the **relationship between e-cigarettes and brain nicotine kinetics.** Age mean years (SD): 43 (13). Sex: 9 males, 8 females. Country: USA Duration of trial: One day. Data source: Participants in each group were recruited from the Winston-Salem, North Carolina area Population size: 17. Year of data collection: Not reported E-cigarette, smoking and other related status: E-cigarette users: eight current smokers, eight ex-smokers, and one never-smoker in the e-cigarette group Outcomes: nicotine delivery to the brain Intervention and research design: Not clearly stated but interventions (in the form of e-cigarettes) were provided and comparison were made with other conventional cigarette users The authors concluded that e-cigarettes can deliver nicotine to the brain with similar rapidity as conventional tobacco cigarettes. Therefore, to the extent that rapid brain uptake promotes smoking reward, e-cigarettes might maintain a degree of nicotine dependence and also serve as non-combustible substitutes for cigarettes.[333] Device and product: Not reported
St. Helen *et al.*[322] 2019	Equal harm	The authors reported on the relationship between e-cigarettes and nicotine exposure in dual users of e-cigarettes and conventional combustible tobacco cigarettes. Age mean years (SD): 21 or older. Sex: 28 males, 8 females. Country: USA Data source: Participants were recruited via Craigslist.com, Facebook, flyers, and college campus newspapers Duration of trial: Two weeks. Population size: 36 Year of data collection: Not reported E-cigarette, smoking and other related status: healthy dual users of e-cigarettes and cigarettes Outcomes: Plasma nicotine was analyzed by gas chromatography–tandem mass spectrometry; nicotine withdrawal, urge to smoke and vape, affective states, craving, satisfaction, and psychological reward were measured by standardized questionnaires Intervention and research design. Compared with findings in conventional usual-brand cigarettes users, maximum plasma nicotine concentration was lower in e-cigarettes users. Both products, (conventional usual brand cigarettes and e-cigarettes) resulted in a reduction in the severity of withdrawal symptoms, negative affect, and urge to use either product. E-cigarettes were less rewarding and satisfying and reduced craving to a lesser degree than cigarettes. Intervention and research design: A two-arm counterbalanced, crossover study over two consecutive weeks. Participants arrived at the Clinical Research Center of the Zuckerberg San Francisco General Hospital between 7:00 to 8:00 AM on Day 5 of each study arm after overnight abstinence starting at 10 PM. At 9:00

Author(s) year	Possible benefit or harm	Interventional trial papers dependency and abuse liability
		AM, participants used the assigned e-cigarette or cigarette in a standardized protocol, taking one puff every 30 seconds; puff duration was not controlled by the study. Cig-a-like and pod users took a total of 15 puffs while fixed-power and variable-power tank users took a total of 10 puffs. Blood samples were collected before and 2, 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the last puff of each product through an intravenous line in the forearm. The authors were not able to detect any differences in withdrawal symptoms, affective states, and urge to smoke cigarettes between e-cigarette and dual users of e-cigarettes and conventional combustible tobacco cigarettes.[322] Device and product: Participants used their usual brands of e-cigarettes and cigarettes, provided by the study.
Vena *et al.*[330] 2020	Harm	The authors reported on the relationship between passive exposure to the use of a female-marketed e-cigarette with selectively enhanced smoking urge, cigarette and e-cigarette desire, and smoking behaviour among women (versus men) smokers. Age mean years (SD): 29.1 (0.7) males, 27.4 (0.8) females. Sex: 31 males, 33 females. Country: USA Duration of trial: One time point. Three duration. Measures gathered up to 50 minutes post intervention. Data source: Candidates were recruited via online advertisements and flyers for a study about “moods, behaviours, and social interactions” to mask the study purpose Population size: 64. Year of data collection: December 2017 and May 2018 E-cigarette, smoking and other related status: daily smoking (5–30 cigarettes per day), not currently attempting to attempting to quit smoking Outcomes: Urge and desire for e-cigarette Intervention and research design: A within- and between-subjects study design in a 1 to 1.5 hours session consisting of a 50-minute cue exposure phase followed by a 50-minute smoking behaviour task. In the cue phase, the participant engaged in two five-minute tasks with another participant separated by a short rest break. The participant then took part in the smoking behaviour phase, which was the latency portion of the Smoking Lapse Task. This component ascertained each participant's ability to refrain from smoking versus obtain a monetary reinforcer. The authors concluded that both women and men were sensitive to the use of the female-marketed e-cigarettes as a smoking cue.[330] Device and product: The control cue was bottled water (16.9 oz. clear plastic bottle). The active cue was a hot pink-coloured iStick Pico e-cigarette mod device adorned with a jewelled crown or bow charm VaporDolls, Etsy).

Table 80: Interventional trial papers on cardiovascular disease, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
Flouris *et al.*[336] 2012	No harm identified	The authors investigated the **acute effects of electronic and tobacco cigarette smoking on complete blood count.** Age mean years (SD): 36.8 ± 9.9 smokers. 28.87 ± 1.5 non-smokers Sex: Smokers-8 males, 7 females. Non-smokers-8 males, 7 females Country: Greece Data source: Two groups of adults volunteered and provided written consent Duration of trial: Twenty-one days. Subjects in each of the two groups participated in three experimental sessions assigned in a random order and separated by a minimum of seven days of wash-out. Blood samples were collected prior to, immediately after, as well as one hour after the active and passive smoking sessions. Population size: 30. Two groups of 15 regarding smoking status, four groups regarding exposure. Year of data collection: Not reported E-cigarette, smoking and other related status: 15 smokers (P15 cigarettes/day) 15 never-smokers. Intervention and research design: The two groups participated in three experimental sessions assigned in a random order and separated by a minimum of seven days of wash-out. The group of smokers underwent a control session (ASCON), an active tobacco cigarette smoking session (ASTOB), and an active e-cigarette smoking session (ASE-CIG). The group of never smokers underwent a control session (PSCON), a passive tobacco cigarette smoking session (PSTOB), and a passive e-cigarette smoking session (PSECIG). All subjects participated in each experimental session once. Blood samples were collected prior to, immediately after, as well as one hour after the active and passive smoking sessions. Prior to each experimental session, each subject was assessed for exhaled carbon monoxide (CO). Values of CO > 15 ppm or reporting by the subject of active smoking or excessive passive smoking in the previous 10 h led to rescheduling of the said session. In the ASCON session, smokers were asked to ‘‘smoke’’ an unlit cigarette of their own brand for 30 minutes. In the ASTOB session, smokers were asked to smoke two tobacco cigarettes of their own brand within 30 min. Finally, in the ASE-CIG session, smokers were asked to smoke a number of puffs on an e-cigarette (device: Giant, Nobacco G.P., Greece) within 30 minutes. The e-cigarette liquid used (Nobacco USA Mix, Nobacco G.P., Greece) had a ‘‘tobacco taste’’ and, according to the manufacturer, incorporated nicotine at 11 mg/ml. The number of e-cigarette puffs for each participant during the ASE-CIG session was calculated as: [(mg of nicotine in own brand of tobacco cigarettes x 1.5 x 50)/11] x 2. Outcomes: white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelet count, mean platelet volume, platelet hematocrit, and platelet distribution width. Moreover, different types of white blood cells – specifically, lymphocytes, monocytes, and granulocytes – were measured as a total count and as a percentage In the Passive smoking session, participants were exposed to normal room air for one hour inside a 60 m3 controlled chamber. In the PSTOB session, participants were exposed to air polluted with tobacco cigarette smoke at a stable CO concentration adjusted at bar/restaurant levels, for 1 hour inside the same chamber. Mainstream smoke was generated from cigarettes by

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		combustion of cigarettes from various popular brands using an air pump set at an air flow rate of 4 l/minute. Cigarettes were half smoked using the air pump and then were left lit for 2 minutes to generate side stream smoke, and then the rest of the cigarettes were smoked. An average of 29.2 ± 0.9 cigarettes was smoked in order to achieve the required level of CO in the exposure chamber. In the PSE-CIG session, participants were exposed to air polluted with e-cigarette vapor for one hour in the same chamber. In this case, a simulated a bar/restaurant e-cigarette smoking environment was achieved by smoking e-cigarettes via the same air pump set at an air flow rate of 4 l/minutes for the same time as in the PSTOB session. The authors concluded that the results suggest that active e-cigarette smoking in smokers and passive e-cigarette smoking in never-smokers do not affect markers of complete blood count. By contrast, active tobacco cigarette smoking in smokers and passive tobacco cigarette smoking in never-smokers increase white blood cell count, lymphocyte count, and granulocyte count for at least 1 hour.[336] Device and product: In the ASE-CIG session, smokers were asked to smoke a number of puffs on an e-cigarette (device: Giant, Nobacco G.P., Greece) within 30 minutes. The e-cigarette liquid used (Nobacco USA Mix, Nobacco G.P., Greece) had a ‘‘tobacco taste’’ and, according to the manufacturer, incorporated nicotine at 11 mg/ml. They were selected for this study because the specific liquid is the only one available in the Greek market that has been analysed by an independent, publicly funded research institute. This analysis demonstrated that the liquid used incorporates >60% propylene glycol, <10% nicotine, <5% linalool, <5% tobacco essence, and <1% methyl vanilyn. It was assumed by the authors of this study that composition of the vapor phase inhaled in this study is similar. The number of e-cigarette puffs for each participant during the ASE-CIG session was calculated as: [(mg of nicotine in own brand of tobacco cigarettes)]
Farsalinos *et al.* [337] 2014b	No harm identified	The authors reported on **the acute effects of using an e-cigarette on myocardial function.** Age mean years (SD): 36 ± 5 Smokers 35 ± 5 E-cigarette users Sex: 32 males 4 females. Country: Greece Duration of trial: One time point. Measures were gathered up to 10 minutes after intervention Data source: The study sample consisted of consecutive healthy subjects visiting hospital for routine examinations who volunteered to participate. Population size: Total 76 smokers males 36 E-cigarette users 40 Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers (group SM) were included if they were smoking for at least 5 years and were consuming at least 15 cigarettes per day. E-cigarette users (group e-cigarette) were included if they had quit smoking and were using electronic-cigarettes with nicotine-containing liquid for at least 1 month, according to self-report. To avoid potential compensatory effects from using lower nicotine-containing liquid, participants were included if they were daily consumers of similar “strength” liquids (9-12 mg/ml nicotine concentration) to that used in the study (11 mg/ml). Intervention and research design: Before and after design. 36 healthy heavy smokers before and after smoking 1 cigarette and 40 e-cigarette users (e-

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		cigarette, age 35 ± 5 years) before and after using the device with "medium-strength" nicotine concentration (11 mg/ml) for 7 minutes. Outcomes: Mitral flow diastolic velocities (E, A), their ratio (E/A), deceleration time (DT), isovolumetric relaxation time (IVRT) and corrected-to-heart rate IVRT (IVRTc) were measured. Mitral annulus systolic (Sm), and diastolic (Em, Am) velocities were estimated. Myocardial performance index was calculated from Doppler flow (MPI) and tissue Doppler (MPIt). Longitudinal deformation measurements of global strain (GS), systolic (SRs) and diastolic (SRe, SRa) strain rate were also performed. The authors concluded that although acute smoking causes a delay in myocardial relaxation, e-cigarette use has no immediate effects. E-cigarettes' role in tobacco harm reduction should be studied intensively in order to determine whether switching to e-cigarette use may have long-term beneficial effects on smokers' health. [337] Device and product: All smokers were asked to use one commercially available tobacco cigarette of the same nicotine (1.0 mg), tar (10 mg) and carbon monoxide (10 mg) yields. E-cigarette users were asked to use a commercially available device with liquid containing 11 mg/ml nicotine concentration. The device used was an eGo-T battery (Nobacco, Athens, Greece) with an eGo-C atomiser (Alter Ego, Athens, Greece). It is considered a "second-generation" device. Unlike cigarette-like devices which consist of a small battery and a polyfil-containing atomiser (commonly called "cartomiser"), the e-cigarette used in this study is a multi-piece system. It consists of a 650 milliampere hour rechargeable lithium battery, delivering 3.5 volts to the atomiser (measured by a volt-meter), and an atomiser consisting of 4 parts: the tank which stores the liquid (capacity of approximately 1.1 ml), the atomiser body, the atomiser head which includes the resistance, and the atomiser cap. It is a manually activated device, by pressing a button; it does not produce any vapour when not activated by the user. The e-cigarette liquid used in the study contained 11 mg/ml nicotine and is considered "medium strength" according to manufacturer's report (USA Mix Med, formerly known as MLB-Med, Nobacco, Athens, Greece). It is sold in 20 ml bottles. It was the only liquid tested by an independent laboratory (National Centre for Scientific Research "Demokritos", mass spectrometry and dioxin analysis laboratory) at the time of study initiation. According to the laboratory report, the contents were: propylene glycol (α -propylene glycol or 1,2-propanediol) in a concentration > 60%, linalool (3,7-dimethylocta-1,6-dien-3-ol) in a concentration < 5%, nicotine (<10%), tobacco essence (<5%), and methyl vanillin (4-hydroxy-3-methoxybenzaldehyde) at < 1%. No tobacco-specific nitrosamines or polycyclic aromatic hydrocarbons were detected. For every participant, a new cartridge and atomiser head was used. One of the researchers filled the cartridge with 1 ml of liquid; subsequently it was positioned in the atomiser and the participant started using it. The battery was fully charged before being used by each subject
Szoltysek-Boldek *et al.*[338] 2014	No harm identified	The authors reported on the **influence of inhaled nicotine from conventional combustible tobacco cigarettes versus e-cigarettes on arterial stiffness.** Age mean years (SD) (range): 23 ± 2 (19 to 25). Sex: All female. Country: Poland Duration of trial: Two study visits separated by at least one day. Total three days in length. Measures were recorded during and 10 minutes post intervention. Data source: Healthy students of the Medical University of Silesia who smoked at least 5 cigarettes per day for at least two years were enrolled in the study.

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Population size: 15. Year of data collection: Not reported E-cigarette, smoking and other related status: All participants reported using e-cigarettes at least 10 times. More specifically they smoked 8±4 cigarettes per day for 4±2 years. Intervention and research design: The study employs a within-subject crossover research design with one day washout period. Every participant visited the laboratory for two experimental sessions. Session 1: participant smoked a conventional cigarette taking 10 to 12 puffs, session 2: participant vaped an e-cigarette taking 15 puffs, sessions 1 and 2 lasted about 1 hour each and were separated by at least one day. Outcomes: A non-invasive measurement of arterial stiffness parameters – Stiffness Index (SI) and Reflection Index (RI) – was conducted and systolic and diastolic blood pressure and heart rate were measured before and after smoking a conventional cigarette as well as use of an electronic cigarette. The authors concluded that in contrast to conventional combustible tobacco cigarette use, the use of e-cigarettes causes no changes in arterial stiffness. They suggested that this may indicate lower bioavailability of nicotine from the e-cigarette or an additional effect of other substances present in cigarette smoke but absent in an e-cigarette aerosol. [338] Device and product: During the study participants used either their regular combustible cigarettes or used e-cigarettes with e-liquid supplied by the research team. The authors used the most common on the Polish market Ego-3 e-cigarettes (Volish Ltd, Poland). The Ego-3 consists of clearomizer Crystal 2 with heating coil of 2.4 Ohm resistance and stabilized voltage battery (900 milliampere hour, 3.4V). Batteries were fully charged for 24 hours before each use. Participants used 24 mg nicotine/mL e-liquid during experiments. Nicotine content in the aerosol generated in laboratory conditions using the automatic smoking machine Palaczbot® [11] was 0.77±0.12 mg (15x70 mL puffs, 1.8 sec. puff durations, and 17 sec. puff intervals). Participants used filtered, 'slim' type combustible cigarettes defined by the manufacturer to have a nicotine content of 0.7 mg per cigarette
Cooke *et al.*[339] 2015	Harm	The authors reported on the **effect of acute inhalation of vaporised nicotine on arterial pressure** in young non-smokers. Age mean years (SD): 23 ± 1. Sex: 10 males, 10 females. Country: USA Data source: Not reported Duration of trial: Two weeks. The interventions were undertaken on two different days separated by at least 1 week. Subjects sat quietly for 10 minutes then had arterial pressure measured subjects then inhaled once every 30 s for 10 minutes, subjects remained seated for an additional then asked to report any symptoms (nausea, lightheadedness, etc.) and had arterial pressures measured again. Urine cotinine concentration was also assessed at this time. Population size: 20. Year of data collection: Not reported E-cigarette, smoking and other related status: healthy non-smoking volunteers Intervention and research design: Experiments were conducted on two different days separated by at least 1 week (randomized, counterbalanced, and double blinded). Subjects then inhaled once every 30 s for 10 minutes from an e-cigarette containing nicotine (18 mg) or a placebo (0 mg nicotine). Data were recorded for 5 minutes with subjects' supine, for 5 minutes in the 70' head-up tilt position, and for a 5-minutes supine recovery. Throughout the experiment, subjects breathed in time with a metronome set at a pace of 15 breaths per minute.

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Outcomes: seated arterial pressures at rest, and on arterial pressure and functional autonomic control during a hemodynamic challenge associated with orthostatic stress. Specifically, arterial pressure, urine cotinine concentration, Electrocardiogram and efferent muscle sympathetic nerve activity from the right peroneal nerve, symptoms (nausea, light-headedness, etc.). After the inhalation protocol, decreases in both heart rate and systolic pressure in the placebo condition, and increases in heart rate and systolic pressure in the nicotine condition (also both p C 0.05), resulted in higher heart rates and systolic pressure for the nicotine compared to the placebo trial. Ranges of urine cotinine concentrations were higher after inhalation on the nicotine compared with the placebo cartridge. efferent muscle sympathetic nerve activity was numerically higher after nicotine inhalation compared with placebo in the supine position, but not statistically distinguishable. After inhaling on the nicotine cartridge for 10 minutes, 19 of 20 subjects reported feeling lightheaded, and 3 subjects also reported nausea. In comparison, no symptoms of physical discomfort were reported by subjects after inhaling on the placebo cartridge The authors concluded that vaporised nicotine inhalation is not harmless[339] Device and product: Nicotine and placebo cartridges were obtained from Green Smart Living (Salt Lake City, UT) and Clean Electronic-cigarettes.
Yan *et al.*[340] 2015	Harm, but less harmful than tobacco cigarettes	The authors reported on the **effects of using e-cigarettes on nicotine delivery and cardiovascular function** in comparison with conventional combustible tobacco cigarettes. Age mean years (SD): 38.7 ± 10.77. Sex: 11 males, 12 females. Country: USA Ethnicity: American Indian/Alaska Native 1 Black or African American 3 White 20 Duration of trial: Eleven days. Subjects participating in the lead-in checked in on Day -2 and remained in the clinic. Subjects abstained from use of nicotine-containing products for a period of at least 36 h prior to each product administration (Days 1, 3, 5, 7, 9, and 11). Days -1, 2, 4, 6, 8, and 10 were designated wash-out days in order to obtain the required 36-hour nicotine-free period between product administrations. Each product administration day included a controlled product administration and a 1-hour ad lib use of the study product. The controlled product administration consisted of 50 puffs of the assigned e-cigarette product (5-s puffs at 30-s intervals) or smoking one Marlboro_ Gold King Size cigarette (30-s intervals with the subjects' normal puff duration) with puff counts monitored by the clinical staff. Blood samples for plasma nicotine, blood pressure, pulse rate, and exhaled CO measurements were obtained at scheduled time points on each product administration day. For blood samples were collected at approximately 10 minutes prior to and at 5, 10, 15, 20, 25, 30, 45, 60, 75, and 90 minutes following the start of the controlled product administration. Cardiovascular vital signs, e.g., systolic blood pressure, diastolic blood pressure, and heart rate, were measured at approximately 30 minutes prior to the start of the controlled product use and approximately 20 minutes following the end of the ad lib product use on Days 1, 3, 5, 7, 9, and 11. Exhaled CO was assessed at approximately 20 minutes prior to the start of the controlled product use and at approximately 15 minutes following the end of the ad lib product use. Data source: Not reported. Population size: 23. Year of data collection: Not reported E-cigarette, smoking and other related status: smoked an average of 10 or more manufactured cigarettes per day for at least 12 months prior to the study.

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Intervention and research design: The study design was a randomized, partially single blinded, six-period crossover study. The interventions or study product were products A to E (detailed below). Each product administration day included a controlled product administration and a 1-hour ad lib use of the study product. The controlled product administration consisted of 50 puffs of the assigned e-cigarette product (5-s puffs at 30-s intervals) or smoking one MarlboroGold King Size cigarette (30-s intervals with the subjects' normal puff duration) with puff counts monitored by the clinical staff. Comparisons were made to evaluate differences between the e-cigarette formulations as well as to the market-leading conventional cigarette, Marlboro_ Gold King Size. Outcomes: Plasma nicotine, Cardiovascular vital signs, e.g., systolic blood pressure, diastolic blood pressure, and heart rate and exhaled CO. The authors concluded that the nicotine plasma concentrations after 1.5 hours of e-cigarette product use were significantly lower in the users of e-cigarettes than in users of Marlboro cigarettes. The combination of glycerine and propylene glycol as the delivery vehicle facilitated delivery of more nicotine than the use of glycerine alone. The heart rate, as well as systolic and diastolic blood pressure, were significantly elevated after use of Marlboro cigarettes, but the elevation was less after use of most of the e-cigarettes tested. Use of e-cigarettes had no impact on exhaled carbon monoxide levels, whereas the Marlboro cigarettes significantly increased exhaled carbon monoxide to more than eight times above the baseline.[340] Device and product: The blu e-cigarettes are currently sold in retail outlets across the United States (US) in both disposable and re-useable forms. The blu e-cigarettess prepared for use in the current study were 2 commercial products (Product D and E) that contain 16 mg/mL (1.6%) nicotine (USP grade), and 3 non-commercial products (Product A, B and C) that contain 24 mg/mL (2.4%) nicotine (USP grade), in the cartomizer device format attached to rechargeable batteries. In comparison, the nicotine yield of the market-leading conventional cigarette (Marlboro_ Gold King Size) is approximately 0.8 mg per cigarette (FTC 2007). As the blu e-cigarettes may yield from 250 to 400 puffs per cartridge, a single cartridge may equate to approximately 1–2 packs of conventional tobacco cigarettes. The following investigational and comparator product designations were used in this study. Product A: Classic Tobacco e-cigarette in rechargeable cartomizer (2.4% nicotine, ~75% glycerine vehicle), or Product A Classic e-cigarette (2.4% Nic in Gly) Product B: Classic Tobacco e-cigarette in rechargeable cartomizer (2.4% nicotine, ~50% glycerin/_20% propylene glycol vehicle), or Product B Classic e-cigarette (2.4% Nic in Gly/propylene glycol) Product C: Magnificent Menthol e-cigarette in rechargeable cartomizer (2.4% nicotine, ~75% glycerine vehicle), or Product C Menthol e-cigarette (2.4% Nic in Gly) Product D: Classic Tobacco e-cigarette in rechargeable cartomizer (1.6% nicotine, ~75% glycerine vehicle), or Product D Classic e-cigarette (1.6% Nic in Gly) Product E: Classic Tobacco e-cigarette in rechargeable cartomizer (1.6% nicotine, ~50% glycerin/_20% propylene glycol vehicle), or Product E Classic e-cigarette (1.6% Nic in Gly/propylene glycol) Product F: Marlboro Gold King Size, or Product F Marlboro cigarette

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		In addition to nicotine, the blu e-cigarettes prepared for use in this study contain vegetable glycerin, natural and artificial flavours, distilled water, citric acid, and propylene glycol.
Antoniewicz *et al.*[347] 2016	Harm	The authors reported on the relationship between **e-cigarettes and an increase in the number of endothelial progenitor cells** in the blood of healthy volunteers. Age mean years (SD): 28.4. Sex: 9 males, 5 females. Country: Sweden Data source: The authors specifically chosen to recruit sporadic smokers as they would better tolerate exposure to ECV than cigarette smoke naïve individuals, thus minimizing the probability of developing sickness or nausea that are usually associated with smoke inhalation. Duration of trial: Two session. One-week interval. Population size: 16. Year of data collection: Not reported E-cigarette, smoking and other related status: healthy seldom smokers (maximum of 10 cigarettes/ month) Intervention and research design: Sixteen healthy seldom smokers were randomized into two groups either exposed or not exposed to 10 puffs of e-cigarette vapor for 10 minutes, in a crossover design. Blood samples were obtained at baseline and 1, 4 and 24 hours following exposure. Outcomes: Endothelial progenitor cells (stem cells mainly derived from the bone marrow and play a pivotal role in the maintenance, differentiation and regeneration of endothelial cells following vascular injury or neogenesis) and microvesicles (cells which can be biologically active in immune responses, thrombosis and inflammation in determine vascular changes). FeNO and Cotinine levels were also assessed. The authors concluded that in healthy volunteers, 10 puffs of e-cigarette vapour inhalation caused an increase in endothelial progenitor cells. This increase was of the same magnitude as that following smoking one conventional combustible tobacco cigarette. Taken together, these results may represent signs of possible vascular changes after short e-cigarette inhalation.[347] Device and product: A popular second-generation e-cigarette device (eGo XL, 1100 milliampere hour, operating at 3,7 V) with a dual-coil CE5 atomizer was used. E-liquid (nicotine 12 mg/ml: propylene glycol 49.4%, glycerine 44.4%, 5% ethanol, 1.2% nicotine) without any added flavouring or aroma (Valeo laboratories GmbH, Germany). The manufacturer has tested this product at an independent laboratory (Eurofins WEJ Contaminants GmbH, Germany) and at the national quality inspection association (TÜV e Technical Inspection Association, Germany). Content analysis is freely available on the manufacturer's homepage[451]
Carnevale *et al.*[342] 2016	Harm	The authors examined the **acute impact of tobacco and e-cigarette smoking on oxidative stress and vascular function.** Age mean years (SD): 28.0 ± 5.3. Sex: 21 females (52.5%). Country: Italy Duration of trial: Two study visits separated by at one week. Measures were gathered just before and within 30 minutes after intervention Data source: Not reported Population size: 40 healthy subjects 20 smokers and 20 non-smokers, matched for age and sex Year of data collection: September 2014 and March 2015

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		E-cigarette, smoking and other related status: For smokers only (n=20) number of cigarettes smoked daily 11.1 (+/-5.8) Intervention and research design: Crossover, single-blind study. The order of assignment of the two types of cigarette that had to be smoked in the two phases of the study was not randomized. All the subjects smoked a tobacco cigarette in the first phase of the study and then smoked an e-cigarette in the second phase of the study Indicators of oxidative stress (serum levels of soluble NADPH oxidase 2 (NOX2)-derived peptide, nitric oxide bioavailability, 8-iso-prostaglandin F2α-III, and vitamin E) and endothelial dysfunction (flow-mediated dilation) were collected. Outcomes: Markers of oxidative stress, nitric oxide bioavailability, vitamin E levels, flow mediated dilation. After having smoked either a tobacco cigarette or an e-Cigarette, significant changes in the levels of sNOX2-dp, 8-isoPGF2a, vitamin E, and NO bioavailability (all, P < .001) were detected in both smokers and non-smokers. There was no significant difference between the groups (3.26 +/-0.57 mm vs 3.29 +/-0.59 mm; P =0 .827) regarding brachial artery diameter at baseline. Changes in flow mediated dilation values were also consistently decreased in all groups after smoking either a tobacco cigarette or an e-Cigarette. No significant changes in flow mediated dilation were seen in a small control group (n = 8, 4 smokers and 4 non-smokers) after smoking a sham cigarette (an e-Cigarette without the cartridge, P =0 .731 for smokers and P = .662 for non-smokers). The authors concluded that smoking both e-cigarettes and conventional combustible tobacco cigarettes led to a significant increase in the levels of soluble NOX2-derived peptide and 8-iso-prostaglandin F2α and a significant decrease in nitric oxide bioavailability, vitamin E levels, and flow mediated dilation.[342] Device and product: In the first phase, all subjects, both smokers (who had not smoked for at least 12 h) and non-smokers, smoked one tobacco cigarette from a leading brand (with a mean nicotine content of 0.6 mg according to the package label). In the second phase, 1 week after the first phase, the same subjects smoked a tobacco-flavoured e-Cigarette from a leading brand (charged with a nicotine cartridge, with a mean nicotine content of 16 mg, equivalent to 250 puffs according to the package label).
Farsalinos *et al.*[348] 2016	No harm identified	The authors reported on the effect of **continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to e-cigarettes.** Age mean years (SD): 44.0 ± 12.5. Sex: 190 males 110 females (baseline) Country: Italy. Duration of trial: 12-month Data source: Eligible participants were enrolled in a prospective 12-month randomised, controlled trial consisting of nine office visits at the University Hospital's smoking cessation clinic (Centro per la Prevenzione e Cura del Tabagismo -CPCT; Università di Catania, Italy). Population size: 300 persons were randomised into the different arms of the trial. Two hundred and twenty-five subjects (75.0 %) returned at week 12, 211 (70.3 %) at week 24, and 183 (61.0 %) at week 52 for the final follow-up visit. Year of data collection: The smokers were recruited during the period June 2010–February 2011 with a final follow-up visit at week 52. E-cigarette, smoking and other related status: The trial registry describes the trial as observational, with a 24-week follow-up, but was conducted as a three-

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		arm randomised controlled trial (RCT) with a 52-week follow-up because the authors decided to monitor the long-term impact of different nicotine levels on smoking cessation or reduction, BP and HR. This is a post hoc analysis, since BP and HR were not officially among the primary or secondary outcomes of trial in the registry entry Intervention and research design: Randomised, controlled trial. Regular smokers not intending to quit were invited to try ECs (''Categoria'', Arbi Group Srl, Italy). Outcomes: Blood pressure and heart rate The authors concluded that quitting smoking with the use of e-cigarettes does not lead to higher blood pressure values, and this is independently observed whether e-cigarettes are regularly used or not[348] Device and product: Participants receive an e-cigarette kit with either ''Original'' (2.4 % nicotine—Group A), or ''Categoria'' (1.8 % nicotine— Group B), or ''Original'' without nicotine (''sweet tobacco'' aroma—Group C) cartridges
Fogt *et al.*[353] 2016	Harm	The authors reported on the **acute cardiorespiratory and performance effects of vaporised nicotine delivered via e-cigarettes at rest and during cycle exercise** in young, normotensive, non-smoking subjects. Age mean years (SD): 23.1 ± 2.5. Sex: 10 males 10 females. Country: USA Duration of trial: Two session. One-week interval. Using a double-blind design, 20 subjects participated in two randomized trials: placebo (0 mg nicotine) or nicotine (18 mg nicotine). Two sessions (trials) separated by one week. Participants were provided a blinded e-cigarette and instructed to inhale deeply once every 30 s over the course of 10 minutes (20 inhalations total). During a 10 minutes quiet rest following use of the EC, participants completed a short questionnaire to assess subjective symptoms from the inhalations. At the conclusion of the 10 minutes rest period, participants provided a urine sample for the assessment of cotinine. Resting metabolic rate was assessed by indirect calorimetry. The incremental cycle test protocol commenced 5 minutes following resting metabolic rate testing to evaluate participants' peak power output and cardiorespiratory response and peak aerobic capacity. Resting metabolic rate was assessed 40 minutes later by indirect calorimetry followed by an incremental cycle test. Data source: Volunteer subjects self-reporting as healthy and non-smoking Population size: 20. Year of data collection: Not reported E-cigarette, smoking and other related status: Intervention and research design: Subjects participated in two randomized trials, double-blind design, separated by ≥1 week: placebo 0 mg•ml-1 nicotine e-cigarette trial and 18 mg•ml-1 nicotine e-cigarette trial. Outcomes: Resting systolic and diastolic blood pressure, resting metabolic rate, heart rate, non-protein respiratory quotient, systolic and diastolic blood pressure during exercise and aerobic power during exercise (cycle exercise (VO2). Expired air was analyzed to estimate whole-body oxygen consumption (VO2; L•min-1). Caloric energy expenditure (kcal•min-1) was then estimated using the thermal equivalents of oxygen for the non-protein respiratory quotient The authors concluded that acute vaporised nicotine inhalation via e-cigarettes increases resting and exercise diastolic blood pressure but does not

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		affect resting metabolic rate or cycle aerobic power in young, normotensive non-smokers.[353] Device and product: A single brand of over-the-counter e-cigarette was used for this study (Green Smart Living, Salt Lake City, UT). The 18 mg and 0 mg e-cigarette cartridges are marketed to vary only in nicotine content.
Vlachopoulos *et al.*[341] 2016	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between **e-cigarette smoking and increases in aortic stiffness and blood pressure** in young smokers. Age mean years (SD): 30 ± 8. Sex: Not reported. Country: Greece (assumed) Duration of trial: Four sessions. Interval period not reported. Measures were gathered up to 60 minutes after intervention. Data source: Not reported. Population size: 24 smokers. Year of data collection: Not reported E-cigarette, smoking and other related status: smokers Intervention and research design: Studied 4 separate occasions (total 96 sessions): 1) simulate tobacco cigarettes (TC) over 5 minutes; 2) Electronic-cigarettes (EC) over 5 minutes; 3) Electronic-cigarettes (EC) for a period of 30 minutes; and 4) nothing (sham procedure) for 60 minutes. Electronic-cigarettes 5 minutes was chosen as a direct comparison with simulate tobacco cigarettes (nicotine delivery rate from Electronic-cigarettes is far lower and slower than with simulate tobacco cigarettes), and Electronic-cigarettes 30 minutes to mimic the common pattern of Electronic-cigarettes smoking (nicotine delivered obtained plasma levels comparable with those after 5 minutes of simulate tobacco cigarettes smoking Outcomes: Carotid-femoral pulse-wave velocity (PWV) was used to assess aortic stiffness and blood pressure The authors concluded that various patterns of e-cigarette smoking on aortic stiffness and blood pressure clearly demonstrated an unfavourable effect. Using e-cigarettes for 30 minutes induces an unfavourable effect on aortic stiffness similar to tobacco cigarette smoking. The influence of e-cigarette smoking for 5 minutes on aortic stiffness is not as prompt (peak effect at 15 minutes) and is less potent compared with the effect of tobacco cigarette smoking.[341] Device and product: Not reported
Moheimani *et al.* [343] 2017	Harm	The authors reported on the role of **nicotine versus non-nicotine constituents in e-cigarette emissions in causing increased resting cardiac sympathetic nerve activity and increased susceptibility to oxidative stress** in otherwise healthy humans. Age mean years (SD): 26.3 ± 0.9. Sex: 13 males, 20 females. Country: USA Ethnicity: 5 Black 8 Asian 5 Hispanic 15 White (non-Hispanic) Duration of trial: Three study visits at four-week intervals. Each participant underwent the each of the 3 exposure sessions, each separated by a 4-week washout. Subjects were studied mid-day (usually between 10:00 AM and 2:00 PM). At commencement of each session the participant was instrumented, blood was drawn, and after a 10-minute rest period, blood pressure and heart rate were measured, and the electrocardiogram was recorded for 10 minutes. The subject then underwent the assigned exposure (e-cigarette with nicotine, e-cigarette without nicotine, or sham control). After repositioning, blood pressure and heart rate were measured, and the electrocardiogram was recorded for 10 minutes, blood was drawn, and the study was concluded

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Data source: Healthy volunteers Population size: 39 participants were enrolled 33 completed the study Year of data collection: Not reported E-cigarette, smoking and other related status: Participants were not current (within 1-year) e-cigarette or tobacco cigarette users or former e-cigarette or tobacco cigarette smokers if they had quit smoking >1 year before the study Intervention and research design: The design is an open-label, randomized, crossover study. In random order, each participant underwent the following 3 exposure sessions, each separated by a 4-week washout: e-cigarette with nicotine; e-cigarette without nicotine (same flavouring and solvent as the "with nicotine" exposure); and sham control consisting of puffing on a device without e-liquid. Outcomes: Heart rate variability, blood tests (paraoxonase-1 activity, (PON-1 activity), low-density lipoprotein oxidizability, and HDL antioxidant/anti-inflammatory capacity, expressed as an HDL antioxidant index, Low-density lipoprotein oxidizability and HDL antioxidant index assays were performed only in participants who used the Greensmoke cigalike device. The authors concluded that the acute sympathomimetic effect of e-cigarettes is attributable to the inhaled nicotine, not to non-nicotine constituents in e-cigarette aerosol, recapitulating the same heart rate variability pattern associated with increased cardiac risk in multiple populations with and without known cardiac disease. Evidence of oxidative stress, as estimated by plasma paraoxonase activity, was not uncovered following acute e-cigarette exposure.[343] Device and product: Fifteen subjects used the Greensmoke cigalike device (the highest rated e-cigarette brand in the United States sold online at the time of the study design28) with tobacco-flavoured liquid, vegetable glycerin/propylene glycol solvents, with 1.2% nicotine and 0% nicotine (on different days) content. After using the Greensmoke cigalike e-cigarette with 1.2% nicotine, only 5 of 15 of the subjects had detectable nicotine and/or cotinine in plasma, so the final 18 subjects used a more- efficient nicotine delivery system, the second-generation penlike device (1.0 O, eGo-One by Joyetech, Irvine, CA), with strawberry flavouring, vegetable glycerin/propylene glycol solvents, with 1.2% nicotine and 0% nicotine (on different days) content. E-cigarette topography was standardized. Participants were verbally cued every 30 seconds with a recording: "Ready, set" (place e-cigarette in mouth), "go, 2, 3" (inhale 3 seconds), "hold, 2, 3" (hold aerosol in), then exhale. No plasma nicotine/cotinine was detectable in the first 6 subjects who used the cigalike device for 10 minutes, so the acute exposure was increased to 30 minutes (60 puffs) for the final 27 subjects.
Chaumont *et al* [345] 2018	Harm	The authors reported on the **differential effects of e-cigarettes (specifically the differential effects of vehicles, propylene glycol and glycerol, and nicotine) on macro and microvascular function, arterial stiffness, and oxidative stress.** Age mean years (SD): 23 ± 0.4. Sex: 18 males, 7 females. Country: Belgium. Data source: Participants were enrolled based on their excellent vaping tolerance. Duration of trial: Three period crossover design. Interval period length not quantified. Vaping sessions (with and without nicotine) consisted of 25 puffs (4-s puffs at 30-s intervals) in order to create sub-ohm vaping. During the sham-vaping session, strict supervision of the participants ensured that they followed exactly the same respiratory manoeuvres, but with the e-cigarette

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		turned off. The timing at which outcomes were measured varied according to outcome but included ongoing measure measurement during the intervention and measurements were made ten minutes before and five-minute after exposure. Population size: 25. Year of data collection: Not reported E-cigarette, smoking and other related status: Healthy occasional tobacco smokers median cumulative pack-year 0.2 [interquartile range 0.1–0.8]) Intervention and research design: This randomized study was placebo-controlled, single-blind with a three-period crossover design. The periods consisted of: 1) vaping without nicotine; 2) vaping with nicotine; and 3) sham-vaping. Blood was drawn 15 minutes before and 30 minutes after vaping (with and without nicotine) or sham-vaping Outcomes: Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress. The primary outcome was the impact of vaping on skin microcirculatory blood flow function (Ach mediated vasodilation). Secondary outcomes included continuous hemodynamic parameters, arterial stiffness and oxidative stress analyses after exposure. Hemodynamic parameters specifically finger systolic and diastolic blood pressure waveforms. Arterial stiffness assessment specifically aortic wave reflection assessment. Central aortic hemodynamics, and augmentation index corrected for heart rate (AIx75), were estimated using pulse wave and wave separation analysis. Oxidative stress and nicotine assessment specifically plasma total myeloperoxidase, protein-bound 3-chlorotyrosine and homocitrulline and plasma nicotine. Neither sham-vaping nor vaping in the absence of nicotine resulted in modifications of cardiovascular parameters or oxidative stress. In contrast, vaping with nicotine: impaired acetylcholine mediated vasodilation, increased indices of arterial stiffness, namely augmentation index corrected for heart rhythm and pulse wave velocity, increased systolic and diastolic blood pressures as well as heart rate and finally; raised plasma myeloperoxidase The authors concluded that their findings demonstrated that high-temperature e-cigarette vehicle vaporisation does not alter micro- and macrovascular function or oxidative stress, and that these effects are solely attributable to nicotine.[345] Device and product: The carrier used in the two e-liquids was a mix of 50% propylene glycol and 50% GLY pharmaceutical grade (Fagron©, Waregem, Belgium). One e-liquid was nicotine free (0 mg.ml−1), whereas nicotine (Nicobrand©, Coleraine, UK) was added to the other one at a concentration of 3 mg.ml−1. A last-generation high-power vaping device with popular and commercially available parts in U.S (Smoke©, Shenzen, China) was used. E-cigarettes were set-up at 60 Watts (0.4Ω dual coils). Vaping sessions (with and without nicotine) consisted of 25 puffs (4-s puffs at 30-s intervals) in order to create sub-ohm vaping conditions
Franzen *et al.*[350] 2018	Harm	The authors reported on the relationship **of e-cigarettes and cigarettes with peripheral and central haemodynamics, as well as arterial stiffness.** Age mean years (SD): 22.9 ± 3.5. Sex: 5 males, 10 females. Country: Germany Duration of trial: A randomized, double-blinded pilot study. Three session with a 48 hour (or more) wash out period between interventions. Generally, measurements were started at least 30 minutes before vaping or smoking. Blood pressure were measured every 5 minutes and with a conventional blood pressure monitor every 15 minutes. Measurements discontinued not less than 2 hours after the application. The three measurements were taken around the same time of day to avoid change due to circadian rhythms.

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Data source: The participants were recruited from students of the University of Lubeck, Germany Population size: 15. Year of data collection: Not reported E-cigarette, smoking and other related status: young, active, conventional combustible tobacco cigarette smokers Intervention and research design: This single-centre pilot study included 15 young, active, conventional combustible tobacco cigarette smokers. The trial was designed as a crossover study of the acute use of three tobacco products. The subjects were blinded to the nicotine content of the e-cigarette. The participants were randomized to one of the three study groups during the first visit by drawing pieces of paper from a closed envelope. An elapse of 48 hours was scheduled between each test day to avoid any acute interaction between devices. The envelope contained three pieces of numbered paper (one to three); participants' order was moved by drawing three times. The numbers denoted e-cigarette with nicotine, e-cigarette without nicotine, or cigarette. The three different study groups were the following: (1) smoking a cigarette and inhaling into the lungs (Cig) (Philip & Morris, New York, USA); (2) vaping an e-cigarette with nicotine (E-cigarette (+)) (DIPSE, eGo-T CE4 vaporizer (third generation), SSR Produkt GmbH & Co KG, Oldenburg, Germany, 3.3 volts, 1.5 ohms and 7.26 watts; 24 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour); and (3) vaping an e-cigarette without nicotine (E-cigarette (–)) (0 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour). Outcomes: Resting blood pressure and resting metabolic rate, and exercise blood pressure and aerobic power. Resting metabolic rate was not different between trials. Compared to the placebo, resting diastolic pressure was 3 mmHg higher with nicotine. VO2peak was not different between the nicotine trial and placebo trials, and Wmax was also similar between nicotine and the placebo. During the cycle exercise test, average diastolic pressure was higher following nicotine use compared with placebo trial, and exercise diastolic pressure peak after nicotine was significantly higher than placebo. Resting systolic blood pressure was lower for nicotine trial but no systolic blood pressure treatment effect was observed during exercise The authors concluded that changes in peripheral and central blood pressure and also in pulse wave velocity after smoking a conventional combustible tobacco cigarette as well as after vaping a nicotine-containing e-cigarette. These findings may be associated with an increased long-term cardiovascular risk.[350] Devices and products: (1) smoking a cigarette and inhaling into the lungs (Cig) (Philip & Morris, New York, USA); (2) vaping an e-cigarette with nicotine (E-cigarette (+)) (DIPSE, eGo-T CE4 vaporizer (third generation), SSR Produkt GmbH & Co KG, Oldenburg, Germany, 3.3 volts, 1.5 ohms and 7.26 watts; 24 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour); and (3) vaping an e-cigarette without nicotine (E-cigarette (–)) (0 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour).
Mastrangeli *et al.*[344] 2018	Harm	The authors reported on the relationship of **conventional combustible tobacco cigarettes and e-cigarettes with oxidative stress and endothelial dysfunction**. Age: Reported by tertials of analysis. Sex: Reported by tertials of analysis. Country: Italy

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Duration of trial: Two study visits. A washout period of one week before first assessment, and again before second assessment. Measures were gathered 'immediately after smoking'. Data source: Not reported Population size: 40 subjects (20 smokers, 20 non-smokers) Year of data collection: September 2014 to March 2015 E-cigarette, smoking and other related status: 20 smokers, 20 non-smokers Intervention and research design: crossover single-blind trial with a week between sessions. 40 subjects (20 smokers, 20 non-smokers) underwent blood draws for measurement of biomarkers. After a washout of 1 month in case of smoking history, 40 subjects (20 smokers, 20 non-smokers) underwent blood draws for measurement of biomarkers, additional blood tests and brachial flow-mediated dilation. Smoking history (time of initiation) and intensity (cigarettes per day) were self-reported, but abstinence was confirmed with a blood cotinine test administered before each experimental smoking session. Specifically, liquid chromatography/tandem mass spectrometry was employed (Quest Diagnostics) with a 3 ng/mL cut-off. They thus were instructed to use either an e-cigarette (charged with a nicotine cartridge, with a mean nicotine content of 16 mg, equivalent to 250 puffs, with subjects taking nine puffs, approximately 0.6 mg of nicotine) or a conventional cigarette (with a mean nicotine content of 0.6 mg). Immediately after smoking, the above measurements were repeated. Subsequently, after an additional wash-out of one week, with abstinence again confirmed with a formal cotinine assay, the same procedure was followed but using the other product to enable within-subject comparisons. Outcomes: Indicators of oxidative stress (serum levels of soluble NOX2-derived peptide, nitric oxide bioavailability, 8-iso-prostaglandin F2α-III, and vitamin E) and endothelial dysfunction (flow-mediated dilation) were collected The authors reported that absolute changes in oxidative stress and vascular features after smoking a conventional combustible tobacco cigarette and vaping an e-cigarette were significantly associated (all $p<0.05$), with the notable exception of 8-iso-prostaglandin F2α-III levels ($p=0.030$). The authors also stated that this post hoc analysis of the SUR-VAPES 1 trial suggests that the comparative oxidative and vascular effects of e-cigarettes versus conventional combustible tobacco cigarettes may be influenced by smoking status, with a potential interaction due to oral contraceptives.[344] Device and product: SUR-VAPES
Nocella *et al.*[354] 2018	Harm	The authors reported on the impact of **conventional combustible tobacco cigarette versus e-cigarette smoking on platelet function.** Age mean years (SD): 28.0 ± 5.3. Sex: 19 males 21 females. Country: Italy Data source: Not reported Duration of trial: Each participant smoked a conventional cigarette then returned 1 week later to vape a study e-cigarette with the same nominal nicotine content. Blood samples were drawn shortly before and 5 minutes after each episode Population size: 40. 20 smokers and 20 non-smokers Year of data collection: September 2014 and March 2015 E-cigarette, smoking and other related status: Healthy participants, 20 smokers and 20 non-smokers

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		Intervention and research design: A crossover single-blind study. The study was divided into 2 phases: in the first phase, all participants, both smokers (who had not smoked for at least 12hours) and non-smokers, smoked one tobacco cigarette from a leading Italian brand (with a mean nicotine content of 0.6mg, according to the package label). In the second phase,1 week after the first phase, the same subjects vaped a tobacco-flavoured E- cigarette from a leading brand (containing a nicotine cartridge, with a mean nicotine content of 16mg equivalent to250 puffs, according to the package label).The subjects vaped for a total of 9puffs (equivalent to 0.6mg of nicotine content) Outcomes: Platelet aggregation, soluble CD40-ligand (sCD40L) and soluble P-selectin (sP-selectin), platelet aggregation. Cotinine concentration. The authors concluded that in smokers, there were no significant changes in sCD40L and sP-selectin, but there was a significant increase in platelet aggregation. In non-smokers, there was a significant increase in all markers of platelet activation following both conventional combustible tobacco cigarette and e-cigarette use. Both conventional combustible tobacco cigarette and e-cigarettes have short-term effects on platelet activation, although in non-smokers the use of e-cigarettes had a less important impact on platelet function.[354] Device and product: The study was divided into 2 phases: in the first phase, all participants, both smokers (who had not smoked for at least 12 hours) and non-smokers, smoked one Tobacco cigarette from a leading Italian brand (with a mean nicotine content of 0.6mg, according to the package label). In the second phase, 1 week after the first phase, the same subjects vaped a tobacco-flavoured e-cigarette from a leading brand (containing a nicotine cartridge, with a mean nicotine content of 16mg equivalent to 250 puffs, according to the package label).
Pywell *et al*.[357] 2018	Harm	The authors reported on the **effect of e-cigarettes on hand microcirculation.** Age mean years (range): 26 years (25 to 27) smokers, 25 (22 to 29 years) non-smokers Sex: Not reported. Country: England UK. Population size: 15 Duration of trial: Two consecutive sessions. Interval not reported. Measures were gathered during and up to 20 minutes post intervention Data source: Smokers and non-smokers were recruited through word of mouth and advertisement posters displayed to staff members of the 2 involved investigative sites within staff-only areas Year of data collection: Baseline and a 12 month follow up point (between June 2015 and March 2017) E-cigarette, smoking and other related status: E-cigarette, smoking and other related status: 7 smokers and 8 non-smokers. The average cigarette consumption of smokers was 1.5 packs per week (0.5e3 packs per week). Smokers were asked to refrain from using any form of nicotine within 4 hours of beginning the study. The control in this study was the baseline microcirculation established over 5 minutes prior to e-cigarette exposure Intervention and research design: Participants commenced a 5-minute smoking protocol of non-nicotine (0-mg) e-cigarettes with continuous microcirculation measurements during smoking and for 20 minutes afterward. The intervention was repeated with nicotine (24-mg) e-cigarettes. A 5-minute smoking protocol of a non-nicotine (0-mg) e-cigarette was then commenced with the participant inhaling from the e-cigarette at a rate of 1 inhalation every 30 seconds, a total of 10 inhalations. Measurements of microcirculation were taken continuously at a rate of 1 per second during smoking and for 20

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		minutes thereafter. In all participants, microcirculation readings had returned to baseline at the end of the 20-minute monitoring period. This was then repeated with the nicotine (24-mg) e-cigarette. Outcomes: Non-invasive O2C laser Doppler probe measured a baseline control reading at deep (7-mm) and superficial (3-mm) levels. A 24-mg e-cigarette significantly reduced smokers' hand microcirculation during and after smoking. Microcirculation increased in smokers after inhalation of a 0-mg e-cigarette. The authors concluded that a 24 mg e-cigarette significantly reduced smokers' hand microcirculation during and after smoking. Microcirculation increased in smokers after inhalation of a 0 mg e-cigarette. The authors advised smokers undergoing hand surgery to avoid high-dose e-cigarettes and, if necessary, to use 0 mg e-cigarettes as an alternative.[357] Device and product: A 5-minute smoking protocol of a non-nicotine (0-mg) e-cigarette was commenced with the participant inhaling from the e-cigarette at a rate of 1 inhalation every 30 seconds, a total of 10 inhalations. This protocol was not tolerated by participants who, on attempting this protocol, developed severe nausea, and therefore, the frequency of inhalations was reduced. It was subjectively agreed among both the investigators and the participants that our protocol mimicked a natural smoking rate.
Spindle *et al.*[351] 2018	Harm	The authors reported on the **effects of the e-cigarette liquid solvents propylene glycol and vegetable glycerine on user nicotine delivery**, heart rate, subjective effects, and puff topography. Age mean years (SD): 18 to 55. Sex: Not reported Country: USA Duration of trial: Participants completed four sessions lasting ~3.5 h and separated by≥48 hours Data source: Potential participants were recruited by advertisements (posted online, throughout campus, and at local vape shops) and word-of-mouth (some participants were informed of the study by other individuals and not via advertisement exposure) Population size: 33. Year of data collection: Not reported E-cigarette, smoking and other related status: E-cigarette-experienced, ≥12-h nicotine- abstinent participants Intervention and research design: Four conditions consisting of two e-cigarette use bouts (10 puffs, 30 seconds interpuff-interval). Participants completed four sessions lasting ~3.5 hours and separated by≥48 hours. Following the one-hour observation period, an intravenous catheter was inserted into a forearm vein of the participant and monitoring of heart rate commenced. Thirty minutes after catheter insertion, a baseline blood sample was taken, and participants completed a "directed" ECIG use bout consisting of 10 puffs with 30 seconds inter-puff-interval. Participants completed a second e-cigarette use bout (60 min after the first) to determine the reliability of the results observed after the first bout. Additional blood samples were taken at 5, 15, 30, 45, and 55 min after the onset of bout 1 and 5, 15, 30, and 45 min after the onset of bout 2. Subjective questionnaires were administered immediately following each blood sampling Outcomes: Nicotine delivery, subjective effects, heart rate, and puff topography were assessed. In the 100 propylene glycol condition, participants took shorter and smaller puffs but obtained significantly more nicotine relative to the two vegetable glycerine (VG)-based conditions. Total nicotine exposure (i.e., area under the curve) was also significantly higher during use of the two-propylene glycol -based liquids. However, participants reported that the 100 propylene glycol liquid was significantly less "pleasant" and "satisfying"

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		relative to the other liquids. Increases in HR and decreases in abstinence symptoms (e.g., "craving") did not differ across conditions. The authors concluded that the ratio of liquid propylene glycol to vegetable glycerine influenced nicotine delivery, some subjective effects, and puff topography. Lower overall product satisfaction associated with the 100% propylene glycol liquid suggests that factors other than nicotine delivery (aerosol visibility) may play a role in maintaining e-cigarette use. Regulating e-cigarette acute effects, such as nicotine delivery, and subjective effects may require simultaneous attention to the ratio of liquid propylene glycol to vegetable glycerine, as well as device, liquid, and behavioural factors known to influence these outcomes. The participants' heart rates increased significantly after use.[351] Device and products: Two E-cigarette-use differing only by liquid propylene glycol :vg ratio (2propylene glycol :98vg, 20propylene glycol :80vg, 55propylene glycol :45vg, 100propylene glycol). Device power (7.3 W) and liquid nicotine concentration (18 mg/ml) remained constant. participants used an "eGo" (3.3 V) battery with a 1.5 ohm, dual-coil, 510 "cartomizer" (7.3 W; SmokTech; Shenzhen, China). "Cartomizers" were filled with 1 ml of E-CIGARETTE liquid ("Virginia Pure" tobacco flavor), containing 18 mg/ml of nicotine (AVAIL Vapor, Richmond, VA). Liquid propylene glycol:vg ratio differed by session. the propylene glycol:vg ratios as labeled by the vendor were: 100:0, 70:30, 30:70, and 0:100. Subsequent independent analysis revealed that the ratios were: 100:0, 55:45, 20:80, and 2:98. Liquid nicotine concentrations were independently verified as ± 1 mg/ml of the labeled concentrations. All "cartomizers" were verified with an Ohmmeter as±0.1 ohm of the purported resistance
Antoniewicz *et al.*[356] 2019	Harm	The authors reported on the **acute effects of e-cigarette inhalation on the vasculature and the conducting airways.** Age mean years (SD): 26 ± 3. Sex: 6 males, 9 females. Country: Sweden Data source: Not reported. Duration of trial: One day Population size: 17 Year of data collection: Not reported E-cigarette, smoking and other related status: 17 healthy occasional users of tobacco products (max ten cigarettes/month), Intervention and research design: randomized, double-blinded, crossover design Volunteers inhaled 30 puffs from the e-cigarette for 30 minutes, with each puff lasting approximately three seconds. Sweden inhaled 30 puffs of e-cigarette aerosol with or without nicotine during a 30-minute period on two separate occasions. The wash out period was a minimum of 1 week. Vascular measurements included systolic and diastolic blood pressure, heart rate, and arterial stiffness and were measured at baseline and following exposure, immediately (0 h), 2 h, and 4 h afterwards. These measurements were performed in 10-minute intervals over 30 minutes. Respiratory measurements included dynamic spirometry, impulse oscillometry, and fractional exhaled nitric oxide (FeNO) and were performed directly following the vascular measurements and additionally at 6-h post-exposure. Outcomes: Vascular measurements included heart rate, systolic and diastolic blood pressure, and arterial stiffness. Pulmonary measurements consisted of dynamic spirometry, impulse oscillometry, and fractional exhaled nitric oxide (FeNO). e-Cigarette aerosol with nicotine caused a significant increase in heart rate and arterial stiffness. Furthermore, e-cigarette aerosol-containing nicotine caused a sudden increase in flow resistance as measured by impulse

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		oscillometry, indicating obstruction of the conducting airways. Both aerosols caused an increase in blood pressure The authors concluded that the present study indicates that inhaled e-cigarette aerosol with nicotine has an acute negative impact on vascular and pulmonary function, and that chronic usage may lead to long-term adverse health effects.[356] Device and product: The e-liquid base consisted primarily of 49.4% propylene glycol, 44.4% vegetable glycerin, and 5% ethanol without any added flavourings (Valeo laboratories GmbH, Germany). Premixed e-liquids with and without added nicotine were used (19 mg/ml and 0 mg/ml resp.). A variable mod third generation e-cigarette was used (eVic-VT, Shenzhen Joyetech Co., Ltd., China). The same settings were used for all exposures (temperature 230 °C, effect 32 W, resistance 0.20 ohm). A dual coil nickel atomizer was used. All exposures were performed in a well-ventilated, temperature-controlled room.
Cossio *et al.*[349] 2020	No benefit or harm	The authors reported on the effects of a **single bout of e-cigarette use on vascular measures of health.** Age mean years (SD): 24 (3). Sex: 9 males, 7 females. Country: USA Duration of trial: Methods not reported. Data source: Methods not reported Population size: 16. Year of data collection: Not reported E-cigarette, smoking and other related status: Tobacco product naïve participants Outcomes: Changes in vascular and haemodynamic measures (blood pressure, cardio-ankle vascular index, flow-mediated dilation) Intervention and research design: three separate "vaping" trials with menthol-flavoured quit smoking aid, electronically heated menthol-flavoured EC with 0% or 5.4% nicotine. During each visit, measurements were performed at baseline, immediately post, 1, and 2 hours post-E-cigarette exposure The authors concluded that there were no significant changes in heart rate, systolic and diastolic blood pressure, endothelial function (via flow-mediated dilation), or arterial stiffness (cardio-ankle vascular index) throughout the experiment.[349] Device and product: Not reported
Sumartiningsih *et al.*[352] 2019	Harm	The authors examined the **exercise-induced heart rate response and heart rate variability in subjects caused by inhaling smoke from tobacco cigarettes and aerosolised vapour from e-cigarettes**. Age mean years (SD): 23.2 ± 1.7. Sex: All males. Country: Indonesia Duration of trial: Each participant was subjected to three different test sessions held at intervals every three days. All participants started their sessions from 9:00 a.m. to 12:00 p.m. After arrival, participants were asked to rest for 5–10 minutes. Next, heartbeat and blood pressure were measured to obtain the baseline data. After the medical examination, participants were asked to smoke EC or TC without knowing the dosage of nicotine, heartbeat and blood pressure were measured immediately after smoking. Participants then performed a maximal multistage 20 m of shuttle run test (MMST). Heart rate and BP were measured again immediately after the MMST test Data source: Male smokers. Duration of trial: Three sessions. Interval 3 days. Population size: 24. Year of data collection: Not reported

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		E-cigarette, smoking and other related status: Regular smoker smoking tobacco cigarette/day (9.2 +/- 1.3 per day). Duration of smoking (year) 3.5 +/- 0.8 Intervention and research design: This study used an experimental design with repeated measures with the same participant and a randomized crossover design (balance order treatment). For each treatment, the participants were assigned to smoke electronic C with zero nicotine/electronic non-nicotine delivery systems (C), electronic-cigarettes with 3 mg/mL of nicotine/electronic nicotine delivery systems (3e-cigarette), and two tobacco cigarettes with 1.5 mg nicotine in each without knowing the nicotine levels. Outcomes: Heart Rate Variability (HR and R wave intervals (RR interval)), Maximal Multistage 20 m Shuttle Run Test (MMST), Time-to-Exhaustion Analyses with maximal oxygen uptake (VO2max) and to assess the time to exhaustion. Heart Rate Variability was evaluated based on the beat-to-beat time interval during the running test. The results showed no statistically significant differences in the run time to exhaustion under the three conditions. Exercise-induced heart rate response as significantly attenuated under the tobacco cigarette condition. The heart rate variability standard deviation of normal-to-normal intervals during exercise significantly increased under nicotine/electronic nicotine delivery systems and tobacco cigarettes. The authors concluded that the results showed that a significant acute autonomic cardiac modulation during exercise is induced by an acute episode of e-cigarette and tobacco cigarette smoking.[352] Device and product: Not reported
Chaumont *et al.*[358] 2020	Harm	The authors reported on the **acute effects of vaping and their reversibility on biological/clinical cardio-respiratory parameters** (serum/urine pneumoproteins, haemodynamic parameters, lung function test and diffusing capacities, transcutaneous gas tensions (primary outcome), and skin microcirculatory blood flow). Age mean years (SD): 38 (2). Sex: All male. Country: Belgium Duration of trial: Three sessions. Interval of seven days between sessions. Data source: Healthy, former tobacco smokers with exclusive nicotine e-cigarette use for at least one year were recruited via a Belgian vaping forum (UBV–BDB–Union-Belge- Pour-La-Vape/Belgische-Damp-Bond) Population size: 30. Year of data collection: January 2018 and November 2018 E-cigarette, smoking and other related status: healthy, former tobacco smokers with exclusive nicotine e-cigarette use for at least one year Outcomes: The following parameters were assessed: transcutaneous O2 (TcpO2) and carbon dioxide (TcpCO2) tensions, respiratory-parameters (pulse oximetry (SpO2), end-tidal CO2, respiratory rhythm), skin microcirculatory blood flow, cutaneous vascular conductance and hemodynamic-parameters (systolic (SBP) and diastolic (DBP) blood pressure, heart rate) Intervention and research design: A randomized investigator-blinded crossover three-periods study was carried out. A minimum of seven days separated each period. The periods included: 1) regular vaping of e-cigarettes containing nicotine for five days and until two hours before the experimental session (nicotine-session); 2) nicotine-free-vaping for five days and until two hours before the experimental session (nicotine-free-session); 3) complete cessation of e-cigarette vaping for five days prior to the experimental session (stop-session). Participants were invited to vape acutely as follows: 1) 10 nicotine puffs at 60W (mean±SEM, 1±0.05g) (acute nicotine-vaping in the nicotine-

Author(s) year	Possible benefit or harm	Interventional trial papers cardiovascular disease
		session); 2) 10 nicotine-free puffs at 60W (1±0.04g) (acute nicotine-free-vaping in the nicotine-free-session); and 3) 10 sham puffs (acute sham-vaping in the stop-session). The authors concluded that short-term e-cigarette cessation by regular users decreases baseline heart rate and lung inflammation and increases forced expiratory flow by 25%, suggesting that high-wattage vaping alters airway function. Urine metabolomic signature was also slightly modified by this short-term e-cigarette cessation. Acute nicotine and nicotine-free vaping decreased transcutaneous oxygen tensions likely as a result of gas exchange disturbances. Finally, only acute nicotine vaping increased systolic blood pressure, diastolic blood pressure, and heart rate.[358] Device and product: A e-liquid base of propylene glycol/glycerol was mixed by the pharmacy at Erasme University Hospital 50:50 v/v; pharmaceutical grade, Fagron©, Waregem, Belgium). One e-liquid lacked nicotine while the other contained nicotine at a concentration of 1.5 mg/mL. Devices included a fourth-generation e-cigarette set at 60 W (Alien 220 box mod, TFV8 baby beast tank and a dual Kanthal coil [V8 Baby-Q2 Core; 0.4Ω dual coils], Smoke©, Shenzen China) with MXJO (Mxjotech©, Shenzen, China) IMR 18650 3000 milliampere hour 35A variable voltage/variable wattage batteries. Airflow was set at the maximum. The manufacturer's recommendations were followed for the preparation of the vaping devices; they were cleaned and filled with e-liquid prior to each exposure. Batteries were fully charged before use, and the coil replaced after two exposures.

Table 81: Interventional trial papers on respiratory diseases, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
Vardavas *et al.*[367] 2012	Harm	The authors reported on the **short-term pulmonary effects of using an e-cigarette, including: impact on respiratory flow resistance, impedance, and exhaled nitric oxide.** Age range: 19 to 56 years. Sex: 14 males, 16 females. Country: Greece Duration of trial: Single session. Measures were recorded soon after the intervention Data source: recruited from a community setting in Athens. Population size: 30 Year of data collection: Not reported E-cigarette, smoking and other related status: all subjects were smokers with a minimum pack-year index of 5 Intervention and research design: Two groups were created: the experimental group (n=30) and the control group (n=10). Ab lib use of an e-cigarette for 5 minutes with the cartridge included (experimental group, n=30) or removed from the device (control group, n=10) was assessed. Outcomes: Lung Function Assessment: Exhaled Nitric Oxide and Dynamic Lung Volumes i.e. spirometry: FVC, L, FEV 1, L, PEF, L/s, maximal expiratory flow (MEF)25, L/s, MEF50, L/s, MEF75, L/s, maximal mid-expiratory flow (MMEF), L/s and Total Respiratory Resistances assessed using impulse oscillometry system (IOS). The authors concluded that the e-cigarettes assessed in the context of this study were found to have immediate adverse physiological effects after short-term use that are comparable to some of the effects seen with tobacco smoking.[367]

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Device and product: The e-cigarettes provided to the subjects were of the same brand (NOBACCO e-cigarettes, black line) and of the same nicotine concentration. The e-cigarette itself was composed of a steel shell, a microprocessor powered by a lithium battery, a filter, and a removable (and renewable) cartridge. Three types of cartridges were available in the market for this e-cigarette, the medium one (NOBACCO MLB-MED filter), for which the manufacturer reports a measured dose of 11 mg of nicotine was used in this study. The e-cigarette cartridge selected for use in the experimental group has been analysed for its chemical composition by the National Centre for Scientific Research, Demokritos, in Greece. According to their analysis, the cartridge contained propylene glycol (a -propylene glycol or 1,2-propanediol) in a concentration 60%, linalool (3,7-dimethylocta-1,6-dien-3-ol) in a concentration , 5%, nicotine (,10%), tobacco essence (,5%), and methyl vanillin (4-hydroxy- 3-methoxybenzaldehyde) at , 1%; no polyaromatic hydrocarbons were detected.
Flouris *et al.*[362] 2013	Harm, but less harmful than tobacco cigarettes	The authors conducted a comprehensive and standardised assessment of the **acute impact of active and passive e-cigarette smoking on serum cotinine and lung function** (plus toxins). Age range: 23.5 to 54 years. Sex: 16 males, 14 females. Country: Greece Duration of trial: Three sessions over a three-week period. Measures were recorded up to one hour after intervention. Data source: Adult. Population size: 30 (15 smokers and 15 never-smokers) Year of data collection: Not reported E-cigarette, smoking and other related status: Fifteen smokers (>=15 cigarettes/day 10–68 pack years) Intervention and research design: Non-randomized repeated-measures controlled study. Each group attended three sessions administered in a random order and separated by a minimum of 7 d wash-out period. All subjects participated in each experimental session once. The group of smokers underwent a control session (ACTIVECON), an active tobacco cigarette smoking session (ACTIVETOB) and an active e-cigarette smoking session (ACTIVEE-CIG), each lasting 30 minutes. In ACTIVECON, smokers were asked to pseudo-smoke an unlit cigarette from a brand of their choice. In ACTIVETOB, smokers were asked to smoke two tobacco cigarettes from a brand of their choice. In ACTIVEE-CIG, smokers were asked to puff an e-cigarette in order to absorb enough nicotine to match two of their favourite tobacco cigarettes as described below. Measurements were conducted before, immediately after, and 1 h after active smoking. The group of never smokers underwent a control session (PASSIVECON), a passive tobacco cigarette smoking session (PASSIVETOB) and a passive e-cigarette smoking session (PASSIVEE-CIG), each lasting 1 h. In PASSIVECON, participants were exposed to normal room air. In PASSIVETOB and PASSIVEE-CIG, participants were exposed to air polluted with tobacco cigarette smoke and e-cigarette vapor, respectively, adjusted to simulate bar/restaurant levels Measurements were conducted before, immediately after and 1 h after each exposure. Outcomes: e-Cigarettes and tobacco cigarettes generated similar (p40.001) effects on serum cotinine levels after active (60.6_34.3 versus 61.3_36.6 ng/ml) and passive (2.4_0.9 versus 2.6_0.6 ng/ml) smoking. Neither a brief session of active e-cigarette smoking (indicative: 3% reduction in FEV1/FVC) nor a 1 h passive e-cigarette smoking (indicative: 2.3% reduction in FEV1/FVC) significantly affected the lung function (p40.001). In contrast, active (indicative: 7.2% reduction in FEV1/FVC; p50.001) but not passive (indicative: 3.4% reduction in FEV1/FVC; p¼0.005) tobacco cigarette smoking undermined lung function.

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		The authors concluded that, regarding short-term usage, the studied e-cigarettes generate smaller changes in lung function than, but a similar nicotinergic impact as, tobacco cigarettes. Future research should target the health effects of long-term e-cigarette usage, including the effects of nicotine dosage.[362] Device and product: e-cigarette device (model: Giant, Nobacco G.P., Greece) within 30 minutes. In the latter session, a new cartridge (within its expiration date) and a fully charged battery were used for each session. Based on its label, the e-cigarette liquid used (Nobacco USA Mix, Nobacco G.P., Greece) had a ''tobacco taste'' and contained 11 mg/ml of nicotine, which is an average concentration since the range of nicotine content in e-cigarette liquids normally range between 0 to 36 mg/ml. Information regarding the e-cigarette device and the liquid used is available at the manufacturer's website (Nobacco G.P., 2012). They were selected for this study because the specific liquid is the only one available in the Greek market that has been analyzed by an independent publicly funded research institute. This analysis, reviewed in detail elsewhere, demonstrated that the liquid used incorporates 46% propylene glycol, 51% nicotine, 55% linalool, 55% tobacco essence and51% methyl vanilyn.
Ferrari *et al.*[363] 2015	Harm, but less harmful than tobacco cigarettes	The authors reported on the **short-term effects of a nicotine-free e-cigarette compared to a conventional combustible tobacco cigarette in smokers and non-smokers.** Age mean years (SD): 39.3 ± 12.6. Sex: 11 males, 9 females. Country: Italy Duration of trial: Two sessions. Interval period 24 hours. The subjects were asked to refrain from smoking in the 6 hours preceding the test session and not to eat or drink for at least 4 hours prior to the experimental procedure. The first smoking session started 5 minutes after the baseline measurement of FeCO, fractional nitric oxide concentration in exhaled breath (FeNO) and pulmonary function tests. The second smoking session started after a wash-out of 24 hours after the end of the first session. The measurements of FeNO, FeCO and pulmonary function tests were repeated immediately after each smoking session. Data source: Normal subjects, recruited among pulmonary fellows or attending physicians were studied Population size: 20. Year of data collection: Not reported E-cigarette, smoking and other related status: 10 were smokers (minimum of 5 pack-years) and 10 were non-smokers. Among smokers' smoke history (pack-years) - mean ± SD (range) 19.4 ± 10.8 (5–35) Intervention and research design: Both smokers and non-smokers were randomized to smoke both the nicotine-free e-cigarette and a commercial "popular brand" standard cigarette ad libitum for 5 minutes in two different sessions according to a crossover design (5 patients within each group smoked first the nicotine-free e-cigarette and then the commercial cigarette and 5 subjects smoked first the commercial and then the nicotine-free e-cigarette). All subjects were asked to use a similar pattern and frequency of smoke aspiration, although it cannot be assured that they did so. The first smoking session started 5 minutes after the baseline measurement of FeCO, Fractional nitric oxide concentration in exhaled breath (FeNO) and pulmonary function tests. The second smoking session started after a wash-out of 24 h after the end of the first session. This wash-out period was to ensure that there was no carry-over effect. The measurements of FeNO, FeCO and pulmonary function tests were repeated immediately after each smoking session. Outcomes: exhaled nitric oxide (FeNO) and fractional concentration of carbon monoxide in exhaled breath (FeCO). Pulmonary function tests: forced vital

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		capacity (FVC), forced expiratory volume in 1 s (FEV1), forced expiratory flow (FEF) 25 %, 50 % and 75 % and peak expiratory flow (PEF). The authors concluded that the specific brand of nicotine-free e-cigarettes used in this study was not associated with major acute physiological changes, causing only small (albeit statistically significant) decreases in forced expiratory flow (FEF) 25% and forced expiratory volume in the first second (FEV1) in the group of smokers. By contrast, smoking a conventional combustible tobacco cigarette induced immediate bronchoconstriction in non-smokers.[363] Device and product: The nicotine-free e-cigarette used in this study, ELIPS C Series (Ovale Europe S.r.l., Desenzano del Garda, Brescia, Italy), was a brand commercially available in Italy. It was formed of a steel shell with a microprocessor powered by a battery, a filter and a removable cartridge. Among the six different types of cartridge available, we chose "Natur Smoke aroma Nocciola Antistress 0 mg/mL nicotina" (Angelica, Bologna, Italy), i.e., a nicotine-free liquid with a hazelnut flavor. The liquid of the cartridge is registered by the Italian Regulatory Agency and had the following composition: glycerine >50 %, isotonic solution 5–10 %, magnesium chloride 1–5 %, natural flavour 0.1–1 %, and vitamin B12 0.1–1 %. The specific kind of nicotine-free e-cigarette chosen in the current study followed an unbiased internet search for products available and produced in Italy (e.g. Dea, Flatech, Flavour Roma). Use of the Angelica liquid was finally decided mainly due to logistic convenience since it was produced in the same city (Bologna) of investigation. The commercial standard cigarette, Marlboro® Red Label Box (Philip Morris USA Inc., Miami, FL, USA), contained nicotine 0.8 mg, carbon oxide (CO) 10 mg and tar 10 mg. According to the manufacturer, the components not exceeding 0.1 % of the weight of the tobacco were acetic acid 0.01, acetophenone 0.0001, ammonium hydroxide 0.3, amyl butyrate 0.0001, benzaldehyde 0.005, benzoin 0.005, benzyl alcohol 0.1, cellulose 9.3, calcium carbonate 4.6, monopotassium phosphate 1.4, potassium citrate 0.3, guar gum 0.1, and hercon 70 0.1.
Campagna *et al.*[359] 2016	Benefit	The authors reported on changes in breathomics from **a 1-year randomised smoking cessation trial of e-cigarettes** fractional nitric oxide concentration in exhaled breath (FeNO), exhaled carbon monoxide, and symptom scores). Age mean years (SD±): 42.9 ± 13.1. Sex: 79 males, 55 females. Country: Italy Duration of trial: One year. Subjects were asked not to smoke/vape for at least 30 minutes prior to each visit. FeNO measurements were taken at baseline and at week 12, week 24 and week 52. Measurements (in ppb) were obtained from a 10-s. exhalation at a steady airflow of 50 mL/s against a flow resistor. Exhaled carbon monoxide measurements were taken at baseline and at each study visits. Measurements (in ppm) were obtained from a single expiratory breath. Self-reported respiratory symptoms in the previous 2 weeks were recorded at baseline and at each follow-up visit. Data source: Not reported Population size: 134 in 3 study arms. Year of data collection: Not reported E-cigarette, smoking and other related status: smoke ≥ 10 tobacco cigarettes per day (cig/day), for at least the past 5 years; Intervention and research design: A prospective 1-year RCT consisting of nine office visits at our smoking cessation clinic. Participants were randomized into three study arms to receive e-cigarette kits with cartridges of identical appearance containing either 2.4% (i.e. 2.4 mg/mL) nicotine (12 weeks of 'Original 2.4%' – Group A) or 1.8% (i.e. 1.8 mg/mL) nicotine (6 weeks of 'Original 2.4%' and a further 6 weeks of 'Categoria 1.8%' – Group B) or no nicotine (12 weeks of 'Original 0%' – Group C)

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Outcomes: FeNO,exhaled carbon monoxide measurements and self-reported respiratory symptoms (cough, phlegm, shortness of breath, wheeze, tight chest, stuffy nose, sinus pain and frontal headache). At baseline, socio-demographic factors, smoking history, Fagerstrom Test for Cigarette Dependence (FTCD) scores were annotated. The authors concluded that smokers who were invited to switch to e-cigarettes who completely abstained from smoking showed steady progressive improvements in their exhaled breath measurements and symptom scores. Fractional exhaled nitric oxide and exhaled carbon monoxide normalisation is highly supportive of improved respiratory health outcomes and adds to the notion that quitting tobacco smoking can reverse harm in the lungs.[359] Device and product: The 'Categoria' EC (model '401') used in this study is a rechargeable three-piece design that closely resembles a conventional cigarette. Disposable cartridges used in this study were of three different types, but of identical appearance: 'Original 2.4%' (2.27 +/-0.13% nicotine), 'Categoria 1.8%' (1.71 +/-0.09% nicotine) and 'Original 0%' without nicotine ('sweet tobacco' aroma). The 'Categoria' EC kit and cartridges were provided free of charge by the local distributor (Arbi Group Srl).
Cibella *et al.*[360] 2016	Benefit	The authors reported on **lung function and respiratory symptoms in a randomised smoking cessation trial** of e-cigarettes, presented on the basis of participants' pooled continuous smoking phenotype classification (quitters, reducers, or failures). Age mean years (SD): 42.2 ± 12.6. Sex: 75 males, 55 females. Country: Italy Duration of trial: One year Data source: Smokers not intending to quit were invited to switch to first generation cigarette-look-a-like ECs ('Categoria', Arbi Group Srl) as a complete substitute for tobacco smoking. Population size: 130 (with available spirometry data) 183 completed the study. Group A N=46 Group B N=43, Group C N=41 Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers not intending to quit. Intervention and research design: 1-year randomized controlled trial of smokers receiving e-cigarettes containing 2.4%, 1.8% or 0% nicotine Outcomes: Spirometric indices as well as in respiratory symptoms: exhaled carbon monoxide, FTND, FEV1, FEV1 (% predicted), FVC (FVC (% predicted), FEV1/FVC, FEF25%–75%, FEF25%–75%. Cough/phlegm, Shortness of breath The authors concluded that this 1-year prospective RCT shows improvements in spirometric indices of peripheral airways, as well as in respiratory symptoms in smokers who were invited to quit or reduce their cigarette consumption by switching to first-generation e-cigarettes. Specifically, the present study shows progressive and consistent improvement in forced expiratory flow (FEF) 25–75% among those who completely gave up cigarette smoking. Improvements in FEF 25–75% from baseline were no different in quitters who stopped using e-cigarettes compared with quitters who were still using e-cigarettes.[360] Device and Product: Categoria', Arbi Group Srl
Dicpinigaitis *et al.*[368] 2016	Harm	The authors reported on the **effect of e-cigarette use on the urge-to-cough** sensation, specifically the urge-to-cough threshold, and cough reflex sensitivity. Age mean years (SD): 29.6 ± 3.2. Sex: 11 males. Country: USA

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Duration of trial: Three sessions on three separate days. Measures were gathered up to 24 hours after intervention Data source: Adult never-smokers. Population size: 17 (30 enrolled into study) Year of data collection: Not reported E-cigarette, smoking and other related status: Non-smokers. Subjects underwent capsaicin challenge testing on Day 1 to establish their baseline urge-to-cough threshold and cough reflex sensitivity. Intervention: On study Day 2 subjects underwent an e-cigarette vaping session subjects inhaled a total of 30 puffs (one puff every 30 seconds) from a disposable e-cigarette (Blu, Classic Tobacco flavour, Lorillard Technologies, Greensboro, NC). Fifteen minutes after the conclusion of the e-cigarette session, subjects underwent capsaicin cough challenge. On study Day 3, approximately 24 hours after the vaping session, subjects underwent repeat capsaicin challenge. In addition, the number of coughs induced by each of the 30 puffs of the e-cigarette was tabulated. A cough number of 5 was assigned for five or more coughs. Intervention and research design: Seventeen healthy non-smokers underwent cough reflex sensitivity measurement employing capsaicin cough challenge at baseline, 15 minutes, and 24 hours after e-cigarette exposure (30 puffs 30 seconds apart) Outcomes: After e-cigarette exposure, urge-to-cough threshold and cough reflex sensitivity were significantly diminished compared to baseline. This effect was transient, as observed by the return of urge-to-cough threshold and cough reflex sensitivity to baseline levels 24 hours after e-cigarette exposure (comparison of baseline urge-to-cough threshold and cough reflex sensitivity 24 hours post-e-cigarette exposure, P = .32). The authors concluded that a single exposure to an e-cigarette significantly inhibits the urge-to-cough threshold as measured by capsaicin cough challenge testing. These findings add to the growing body of evidence that e-cigarette vapour is not a physiologically benign substance and support further investigation of the effects of repeated or chronic use of e-cigarettes on cough sensitivity and other respiratory parameters.[368] Device and product: Disposable Blu e-cigarette contain 20–24 mg of nicotine and delivers approximately 400 puffs of nicotine-containing vapor. The ingredients of the vapor include distilled water, nicotine, vegetable glycerin, natural flavours, artificial flavours and citric acid. Thus, 30 puffs of the e-cigarette delivered approximately 1.5–1.8 mg of nicotine. In comparison, the estimated nicotine intake from a tobacco cigarette is in the range of 1.07–2.6 mg, depending on the brand
Kumral *et al.*[369] 2016	Harm	The authors reported on the impact of **e-cigarette smoking on sinonasal symptoms and nasal mucociliary clearance.** Age mean years (SD): 33.9 ± 7.9 Group 1 38 ± 8.2 Group 2 Sex: 24 males, 18 females Group 1: 16 males, 14 females Group 2 Country and ethnicity: Turkey Duration of trial: One session. A saccharin granule was placed 2 cm inside the right nostril lateral to inferior turbinate by the tester. They were instructed to swallow every 30 s per minute with a chronometer. The time when the subjects first precepted the sweet taste of the saccharin were recorded in minutes Data source: This study was conducted at the Department of Otorhinolaryngology-Head and Neck Surgery. All patients admitted to smoking cessation clinic for a month were enrolled in the study.

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Population size: Total 98. Group 1 42 Group 2 30. However, sixteen patients in the group 1 and ten patients in the group 2 who cannot stop smoking were excluded from the study. Year of data collection: March 2013 and November 2013 E-cigarette, smoking and other related status: Patients smoked one pack of cigarettes per day for at least 5 years. All patients were willing to quit smoking. The mean duration of smoking was 13.5 ± 6.5 years, Intervention and research design: Prospective randomized single-blind clinical trial Outcomes: Changes in sinonasal symptoms and mucociliary clearance assessed by saccharin transit time Patients participating in the study were randomly divided into two groups; e-cigarette smokers (group 1) and non- e-cigarette smokers (group 2). E-cigarette - smokers (n = 58) were the smokers who started e-cigarette to quit smoking. Non-e-cigarette smokers (n = 40) were the smokers who quitted smoking without the aid of medical therapy and a device. Non-e-cigarette smokers had cognitive behavioral treatment during the course. The authors concluded that although e-cigarettes are widely used as a method of quitting smoking, they have negative effects on sinonasal symptoms and mucociliary clearance.[369] Device and product: In this study, patients were allowed to select the brand of the device and flavour of the cartridge. Liquid in the cartridge contained alkaloids fluid with propylene glycol, ethanol, water, tobacco flowers, essential oil, consists of nicotine. Light Cigarettes in the markets have 0.7 mg nicotine per stick. Consuming all 20 cigarettes in a pack will give 14 mg nicotine. For this reason, the authors chose a medium density (11- 12 mg/ml) liquid for this study. The same density as for light cigarette users
Boulay *et al.*[361] 2017	No harm or benefit	The authors reported on the acute **effects of nicotine-free and flavour-free e-cigarette use on lung functions** in healthy and asthmatic individuals. The authors designed a crossover and placebo-controlled trial to investigate the impact of a 1-hour acute vaping session of nicotine-free and flavour-free e-liquid on the pulmonary functions and respiratory mechanics of healthy and asthmatic individuals. Age range: 20 to 37 years Healthy volunteers, 21 to 40 years asthmatic volunteers Sex: Not reported. Country: Canada Data source: Healthy volunteers and ten asthmatic volunteers were recruited for the trial. Duration of trial: Two sessions. Interval one week. The experimental and placebo sessions took place 1 week apart. A preceding visit was also planned, where baseline measurements were taken. On the following two sessions (experimental and placebo), volunteers were asked to inhale three times per minute, in sitting position, for a total duration of 1 hour. Respiratory mechanics and lung functions were measured immediately before (T0), immediately after (T60), and 30 minutes after (T90) the inhalation sessions. Respiratory symptoms were collected according to the Borg perception scale at the same time points as well as every 20 minutes during the inhalation session. The fraction of exhaled nitric oxide (FeNO) and serum C-reactive protein were measured in asthmatic volunteers. FeNO and serum samples were not collected in non-asthmatic volunteers. Population size: 20. Year of data collection: Not reported

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		E-cigarette, smoking and other related status: All volunteers were non-smokers, and none were active e-cigarette users. Moreover, none of the volunteers were exposed to secondary tobacco or e-cigarette vapers at home. Asthmatic volunteers had received a diagnosis of asthma and had airway hyperresponsiveness as shown by a positive methacholine challenge Intervention and research design: This was a crossover and placebo-controlled trial. Volunteers were asked to inhale three times per minute, in sitting position, for a total duration of 1 hour. The experimental and placebo sessions took place 1 week apart. Outcomes: Symptoms, vital signs, lung function and inflammation parameters. Symptoms included: cough, chest tightness, breathlessness, secretions, wheezing, heart rate (beat/min), saturation (% O2), respiratory rate (respiration/min)). Spirometry (forced expiratory volume in 1 second (FEV1) (L) forced vital capacity (FVC) (L) FEV1/FVC. Forced oscillation technique (FOT) R5(forced oscillation technique) at 5 minutes (cm H2O.s/L), R19 (cm H2O.s/L), R5–19 (cm H2O.s/L), X5 (cm H2O.s/L), resonant frequency (Fres) (Hertz), reactance area (Ax) (cm H2O/L/saHz), inspiratory capacity (IC) (L), tidal volume (TV) (L), exhaled nitric oxide (FeNO) (ppb), C-reactive protein (mg/L) The authors concluded that this study shows that a 1-hour inhalation session of a high-grade and contaminant-free mixture of propylene glycol and glycerol using a commercially available e-cigarette, performed in a controlled environment, does not significantly impact pulmonary function or symptoms in either healthy or asthmatic subjects.[361] Device and product: The e-liquid consisted of a mixture of 70% USP-grade propylene glycol and 30% USP-grade glycerol, mixed in our laboratory under a biosafety cabinet. The author claimed this 70% propylene glycol /30% glycerol mixture is largely representative of what is used on the market to dissolve nicotine and/or flavours
D'Ruiz *et al.*[364] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between **partial or complete substitution of cigarettes with e-cigarettes** in adult smokers with measurements of cardiovascular and pulmonary function endpoints and other physiological effects. Age mean years (SD): ~38. Sex: 65% males, 35% females. Country: USA Ethnicity: American Indian/Alaska Native =1, Black or African American =17, Black or African American =1, American Indian/Alaska =1, Hispanic or Latino =1, White=84. Duration of trial: Six days. Subjects checked into the clinic on Day -2 and continued to smoke their usual conventional combustible tobacco cigarette brand ad libitum through the evening of Day -1 (baseline). Participants completed several different questionnaires that measured nicotine dependence and a variety of subjective smoking-related effects over the course of the five-day study. On the morning of Day 1, subjects were randomized into one of six groups (N = 15 each). With limited exceptions, all product use was ad libitum from 07:30 to 23:00 on Days -2 to 5. These exceptions included meals and questionnaire administration, 15 min prior to blood sampling and vital sign measurements, and 30 minutes prior to and during spirometry and exhaled CO and nitric oxide (NO) measurements. Cardiovascular vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate) were measured at least 5 minutes of rest, prior to the start of product administration at ~6:45 in the morning and at ~17:50 in the evening at on Days -1 through 5. All measurements were preceded by a 30-minutes (minimum) abstention from study product use. Spirometry measures of the volume of air exhaled during a forced breath in one second (Forced Expiratory Volume - FEV1) and total volume of air exhaled

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		(Forced Vital Capacity e FVC). Baseline (Day -1) versus post-Baseline (Day 5) changes in FVC and FEV1 spirometry endpoints were performed in the afternoon on Days -1 and 5. Exhaled CO and NO were measured during the study in the afternoon on Days -1 (Baseline), 1, 3 and 5 (prior to spirometry measurements on Days -1 and 5). All physiological measurements were preceded by a 30-minutes (minimum) abstention from study product use. Data source: Not reported. Year of data collection: Not reported Population size: n=105. Exclusive E-Cigarette Use Groups: Tobacco Rechargeable (n=15) Cherry Rechargeable(n=15) Cherry Disposable (n=15) Dual Use Groups Tobacco Rechargeable Cherry Rechargeable (n=15) Cherry (n=15) Disposable Nicotine Cessation (n=15) E-cigarette, smoking and other related status: Baseline cigarettes smoked per day ranged from ~15 to ~21 and years smoked ranged from ~15 to ~22. Menthol smokers made up 37% of the subject population Intervention and research design: Randomized, open-label, forced-switch parallel arm study conducted at a single independent research center. Baseline assessments occurred from the morning of Day -1 through the morning of Day 1 prior to the start of randomized product use and post-baseline assessments on the morning of Day 1 through the morning of Day 6. On the morning of Day 1, subjects were randomized into one of six groups (N = 15 each): Outcomes: Cardiovascular physiology (systolic and diastolic blood pressure and heart rate, pulmonary function (FVC, FEV1, and exhaled CO and NO) and adverse events. All adverse events that occurred during this clinical trial were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 17.1. The authors concluded that use of e-cigarettes for 5 days under the various study conditions did not lead to higher blood pressure or heart rate values, negative respiratory health outcomes, or serious adverse health events. Reductions in blood pressure and heart rate vital signs were observed in most of the participants who either ceased tobacco and nicotine product use altogether or switched completely to using e-cigarettes. Pulmonary function tests showed small but non-statistically significant improvements in forced vital capacity (FVC) and forced expiratory volume in the first second measurements in most usage groups. Statistically significant (p<0.05) benefits associated with smoking reduction were also noted in exhaled carbon monoxide and fractional nitric oxide concentration in exhaled breath. All studied products were well tolerated. The study findings suggest that there are potential cardiovascular and pulmonary function benefits when smokers switch to using e-cigarette products.[364] Device and product: Exclusive e-cigarette Use Groups Group A1 e Tobacco flavour rechargeable blu™ e-cigarette Group A2 e Cherry flavour rechargeable blu™ e-cigarette Group A3 e Cherry flavour disposable blu™ e-cigarette Dual Use Groups Group B1 e Tobacco flavour rechargeable blu™ e-cigarette + usual brand combustible tobacco cigarette Group B2 e Cherry flavour rechargeable blu™e-cigarette + usual brand combustible tobacco cigarette Group B3 e Cherry flavour disposable blu™ e-cigarette + usual brand combustible tobacco cigarette Cessation Group _ Group C e Complete tobacco and nicotine product cessation
Chaumont *et al.* [370]	Harm	The authors reported on the relationship of **high-wattage e-cigarettes with tissue hypoxia and lower airway injury.**
2018b		Age mean years (SD): 23 6 ± 0.4. Sex: 16 males, 7 females. Country: Belgium

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Duration of trial: Two sessions 7 days apart. Time points at which measure were assessed is not specified. Data source: healthy occasional smokers. Population size: 23 Year of data collection: Not reported E-cigarette, smoking and other related status: Participants were enrolled on the basis of their excellent vaping tolerance Intervention and research design: Participants were exposed to 25 puffs of a propylene glycol/glycerol mix (50:50) vaporized at 60 W (V8 Baby-Q2 Core; Smoke; mean liquid volume vaporized, 260.1 ml), to create a real subohm vaping exposure, and to sham vaping (same procedure with e-cigarette turned off). Outcomes: Measure of respiratory and microcirculatory functions and microcirculatory blood flow regulation including measured of skin tissue hypoxia, serum CC16 (club cell protein 16) (a measure of lower airway injury), forced expiratory flow (measure of airway resistance), forced expiratory flow, forced mid-expiratory flow rate, skin continuous microcirculatory flow measured with the thermostatic probe, skin vasodilator responses to acetylcholine, plasma oxidative stress biomarkers The authors concluded that although endothelial microvascular function and oxidative stress remained unaffected, acute vaping of an aerosol of propylene glycol/glycerol at high wattage and in a large amount induced sustained tissue hypoxia, airway epithelial injury, and small airway constriction.[370] Device and product: A propylene glycol/glycerol mix (50:50) vaporized at 60 W (V8 Baby-Q2 Core; Smoke; mean liquid volume vaporized, 260.1 ml), to create a real subohm vaping exposure (3), and to sham vaping (same procedure with e-cigarette turned off).
Coppeta *et al.*[365] 2018	Harm, but less harmful than tobacco cigarettes	The authors examined whether the **active use of e-cigarettes** in healthy subjects can cause **short-term effects on lung function**, and whether these effects are different from those associated with a similar exposure to tobacco smoke. Age mean years (SD) (range): 32.6 ± 2.75 (27 to 37). Sex: 17 males, 13 females Country: Italy Duration of trial: Two study visits. Interval period not qualified. Measures were gathered up to 60 minutes post intervention. Data source: Healthy non-smoking volunteers. Population size: 30. Year of data collection: Not reported E-cigarette, smoking and other related status: Thirty healthy non-smoker volunteers Intervention and research design: Before and after a 5-minute smoking session performed in two different days (first-day e-cigarette, second-day tobacco cigarette. Each participant underwent, in different days, a 5-minute session of active e-cigarette or tobacco cigarette smoking. All participants performed in different sessions both e-cigarette (first session) and tobacco cigarette (second session). Outcomes: For lung function: Forced Vital Capacity (FVC); forced expiratory volume in the first second (FEV 1 or FEV); Index Tiffenau (FEV1/FVC; Peak Expiratory Flow (PEF); forced expiratory flow at 25% of FVC (FEF25%); forced expiratory flow at 50% of FVC (FEF50%); forced expiratory flow at 75% of FVC (FEF75%); forced expiratory flow between 25% and 75% of FVC (FEF25% -75%). For environmental impact: measurement of the concentration of airborne dust with the use of Optical Particle Counter (OPC) model AEROTRAK 9306 of TSI. Measurement of the concentration of airborne dust every second with

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Condensation Particle Counter (CPC) PTrak Ultrafine Particle Counter Model 8525 TSI. Evaluation was performed at baseline, during active smoking and for 60 minutes thereafter. Changes in the main respiratory parameters were significantly different than baseline after 1 minute from e-cigarette smoking (3,95 vs 3,91 lt for FEV:P=0,03; 0,84 vs 0,83 for FEV1/FVC ratio:P=0,008; 4,23 vs 3,99 lt/min for FEF25%-75%: P=0,03) but not after 15 minutes from active e-cigarette smoking, whereas after tobacco cigarette smoking, there was a significant drop in the 15 minutes value of FEV1(P=, FEF25%-75% (P=0.01) and the FEV1/FVC ratio (P=0.007). Regarding environmental exposure, the e-cigarette smoking was associated with the transient release of particles with a diameter < 1 micron which dropped to baseline after 5 minutes, whereas in the case of tobacco cigarette, the particles persisted for 60 minutes. The authors concluded that the active use of e-cigarettes for a short time caused similar, although less pronounced, effects as tobacco smoke on pulmonary function. Similarly, the particles released in the environment had a lower concentration and persistence than those of tobacco cigarettes. These data suggest that e-cigarettes may potentially be dangerous for active smokers and the environment.[365] Device and product: The e-cigarette model was a popular model EGO P (L) with manual start; the liquid used, the aroma of Latakia tobacco containing nicotine 1.8% (18 ml / L), propylene glycol, glycerol, vegetable flavourings, and deionized water. The volunteers were asked to smoke the e-cigarette over 5-minutes time (the same time required for volunteers smoking a conventional combustible tobacco cigarette), performing 15 puffs. The used e-cig had a composition equal to 0.6 mg of nicotine, tar 8 mg and carbon monoxide (CO) 9 mg.
Lappas *et al.*[371] 2018	Harm	The authors investigated the duration of **immediate respiratory effects of e-cigarette smoking** and tested the hypothesis that e-cigarette smoking has more prominent effects in asthmatics compared with healthy smokers. Age mean years (SD): 23.0 ± 3.2. Sex: 33 males, 21 females. Country: Greece Duration of trial: Three consecutive sessions (screening, control, experiment) . Measures were gathered up to 30 minutes post intervention Data source: Not reported. Population size: 54 smokers, 27 healthy smokers and 27 with intermittent asthma Year of data collection: Not reported E-cigarette, smoking and other related status: Intervention and research design: A control session (no liquid, no resistor coil inside e-cigarette cartridge) and an experimental session of ECS using standardized puffing settings. Impulse oscillometry impedance (Z), resistance (R), reactance (X) and fractional exhaled nitric oxide (FeNO) were measured before and 0, 15 and 30 minutes after control and experimental sessions. All participants individually completed three consecutive sessions: screening, control (C) and experimental (E). Outcomes: Impulse oscillometry impedance (Z), resistance (R), reactance (X) and fractional exhaled nitric oxide (FeNO) were measured before and 0, 15 and 30 minutes after control and experimental sessions. The authors concluded that the present study provides evidence that a single session of e-cigarette smoking had immediate mechanical and inflammatory respiratory effects in healthy smokers and in asymptomatic smokers with intermittent asthma. These actions persisted for 15 (International Organization for Standardization methods) to 30 minutes (fractional nitric oxide concentration

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		in exhaled breath). The intensity and duration of these changes were more prominent in the individuals with intermittent asthma.[371] Device and product: All participants used the same new-generation e-cigarette (adjustable voltage) and liquid with 12 mg/mL nicotine concentration. Analysis of the e-liquid using gas and liquid chromatography-mass spectrometry techniques10 showed it contained propylene glycol 46.13% w/v, glycerol 34.3% w/v, nicotine 1.18% w/v and tobacco essence (<5% w/v).
Staudt *et al.*[372] 2018	Harm	The authors reported on the **altered lung biology of healthy never-smokers following acute inhalation of e-cigarettes.** Age mean years (SD): 40.2 ± 9.7. Sex: 5 males, 5 females. Country: USA Duration of trial: Two sessions (control, experiment) Upon study enrolment, participants were assessed on day 1 (baseline) for vital signs (blood pressure, temperature, heart rate, respiratory rate), O2 saturation, chest X-ray, lung function, plasma endothelial microparticles and bronchoscopy with brushings to sample the small airway epithelium and bronchoalveolar lavage to obtain alveolar macrophages (AM) at baseline. One week later, subjects were trained how to use EC then inhaled 10 puffs of "Blu" brand EC, waited 30 minutes, then inhaled another 10 puffs. Immediately after the 1st and 2nd EC exposures, the questionnaires were administered and vital signs and O2 saturation were assessed. Within 2 h post the 2nd EC exposure, lung function, plasma EMPs and repeat bronchoscopy with brushing and lavage were obtained. Data source: Not reported Population size: Total cohort of n = 10, Of the n = 10 total subjects, n = 7 were randomized to Blu EC with nicotine and n = 3 to Blu EC without nicotine. Year of data collection: Not reported E-cigarette, smoking and other related status: healthy never-smokers with no history of exposure to any tobacco products or EC, Intervention and research design: Never smokers were assessed at baseline for outcomes of interest. One week later, subjects inhaled 10 puffs of "Blu" brand EC, waited 30 minutes, then another 10 puff; n = 7 were randomized to EC with nicotine and n = 3 to EC without nicotine to assess biological responses in healthy, naive individual Outcomes: Pulmonary function: FVC (% predicted), FEV1 (% predicted), FEV1/FVC (% observed), TLC (% predicted), DLCO (% predicted), O2 saturation, bronchoalveolar lavage % recovery, Total cells recovered: epithelial cells, macrophages, lymphocytes, neutrophils, eosinophils, small airway epithelium, epithelial cells, inflammatory cells, ciliated cells, secretory cells, undifferentiated cells, basal cells. The authors concluded that the data in the present study suggest that even limited, acute exposure to e-cigarette aerosols dysregulates the biology of the human lung in vivo. Whether or not chronic exposure to e-cigarettes will result in lung disease is unknown and can only be evaluated by large-scale, long-term trials of individuals who are not former or current cigarette smokers who have used only e-cigarettes, a study that would be challenging to carry out at present, as most e-cigarette users have had prior or current cigarette smoke exposure. However, the observed changes in the biology of the small airway epithelium, alveolar macrophages, and (indirectly) lung capillary endothelium may signal that e-cigarette use may not be as safe as has been assumed.[372] Device and product: "Blu" brand EC
Barna *et al.*[366]	Harm, but less	The authors aimed to examine the **effects of combustible and non-combustible methods of smoking on lung function** based on functional respiratory tests and

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
2019	harmful than tobacco cigarettes	the degree of alveolocapillary membrane damage, measured by dynamic inhalation scintigraphy. Age range: 20 to 64 years. Sex: All male. Country: Hungary Duration of trial: Two session periods over two weeks. Measures were assessed on the seventh day of each session. Data source: Healthy cooperative male volunteers. Population size: 24 Year of data collection: Not reported E-cigarette, smoking and other related status: Heavy smokers in the past who regularly used e-cigarette containing at least 10 mg nicotine/ml at the time of examination Intervention and research design: Every volunteer underwent a baseline examination to assess respiratory function on regular e-cigarette use. The authors then asked participants to return to normal cigarette smoking for a week consuming at least 20–25 cigarettes/day. There were no smoking-free days between the two types of cigarette use. The second examination was performed after 7 days of conventional combustible tobacco cigarette smoking. Outcomes: Respiration tests [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak expiratory flow rate (PEF), Tiffeneau-Pinelli index (FEV1/FVC)] and carbonmonoxide and carboxyhemoglobin concentrations from exhaled air and scintigraphy. Outcomes: Level of carbonmonoxide and carboxyhemoglobin were significantly increased after conventional combustible tobacco cigarette use (P< 0.001). Among respiratory parameters, FVC and FEV1 were decreased after conventional combustible tobacco cigarette use (P <0.05, paired t-test), but we could not find significant changes in PEF, and Tiffeneau-Pinelli index. The clearance of the inhaled radioaerosol through the lungs became significantly faster after conventional combustible tobacco cigarette use compared with e-cigarette smoking on the individual basis. The CTI/2 values calculated from DIS were significantly lower in patients with smoking conventional combustible tobacco cigarette compared with e-cigarette users (P<0.001). the clearance rate was significantly faster in the right lung after 1 week of conventional combustible tobacco cigarette smoking, but there was no difference between the right and left lung on the baseline study. The authors concluded that e-cigarette smoking is less harmful to lung function than conventional combustible tobacco cigarette smoking, and that it can be recommended to heavy smokers who are unable to stop smoking.[366] Device and product: Not reported
Chatterjee *et al.*[373] 2019	Harm	The authors reported on the **acute response to aerosol inhalation of non-nicotinised e-cigarettes** in terms of oxidative stress and indices of endothelial activation in **human pulmonary microvascular endothelial cells**. Age mean years (SD): 28.7 (5.5). Sex: both sexes. Country: USA Trial duration: Two sessions. Seven-day interval. Data source: Subjects were selected from a pool of individuals who had participated in previous trials in the Department of Radiology and who had also agreed to be contacted for possible participation in future trials Population size: 10. Year of data collection: Not reported E-cigarette, smoking and other related status: Non-smokers Outcomes: Biomarkers of inflammation C-reactive protein and soluble intercellular adhesion molecule and nitric oxide metabolites

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		Intervention and research design: Subjects were instructed to drag and inhale in a standardized fashion in the presence of the research coordinator. The paradigm consisted of 16–17 inhalations or puffs, each 2 s long, during which subjects did not breathe in through the nose. The total time spent on the entire protocol (including inhalation, release of vapor, and a few seconds between puffs) was ~3 minutes and is equivalent to smoking an entire conventional cigarette. Overall, the protocol represents the average e-cigarette puffing topography in young adults The authors concluded that the findings suggest that even in the absence of nicotine, acute e-cigarette aerosol inhalation leads to a transient increase in oxidative stress and inflammation. This can adversely affect the vascular endothelial network by promoting oxidative stress and immune cell adhesion. Thus, e-cigarette inhalation has the potential to drive the onset of vascular pathologies.[373] Device and product: E-puffer exhaled carbon monoxide-disposable e-cigarettes were purchased from E-Puffer (New York, NY). E-puffer was chosen as it is a brand of non-nicotinized e-cigarette that is popular among young adults. Other brands that are popular lacked nicotine-free versions. The device consists of a cylindrical lithium battery that supplies 3.7 V to a dual-coil atomizer (heating coil) with a resistance of 2.7 ohms. The liquid tank attached to the atomizer is 1.3 ml in volume and is filled with e-liquid composed of 70% pharma-grade propylene glycol (PG) and 30% vegetable glycerine (VG). The atomizer temperature in a similar device has been reported to vary between 145 and 334°C
Kerr *et al.*[374] 2019	Harm	The authors reported on the acute **effects of electronic and tobacco cigarettes on vascular and respiratory function** in healthy volunteers; this was a crossover study. Age mean years (SD): mean age 31.6 ± 10.5. Sex: All male. Country: UK Duration of trial: Two sessions. All participants attended for two study visits at the same time of day, with a minimum of 24 h between each visit. The number of days between study visits was six but ranged ~ 1 to 13 days. Prior to each study visit participants were asked to fast for a minimum of 4 h and to refrain from tobacco smoking, e-cigarette use and from consuming caffeinated and alcoholic products for 12 h. Participants were exposed to each intervention (either tobacco cigarette smoking or e-cigarette use) on separate study days. Study investigations were performed preintervention and post intervention. Three repetitive BP recordings were taken and the mean SBP and DBP recordings were calculated. Post-intervention BP measurements were taken 10 minutes following the intervention. Heart rate (HR) was measured immediately before and 1 minutes following the intervention. Reactive hyperaemia index (RHI), a measure of endothelial function via peripheral arterial tonometry (PAT); and augmentation index, a measure of arterial stiffness, were assessed. Baseline pulse wave amplitude (PWA) was measured for 5 minutes. The BP cuff was then rapidly inflated on the experimental arm 60mmHg and SBP (the occlusion pressure did not exceed 200mmHg) for a duration of 5 minutes. After exactly 5 minutes of occlusion the BP cuff was rapidly deflated to induce flow mediated reactive hyperaemia. A post occlusion recording was then measured for a further 5 minutes. Postintervention PAT was recorded 15 minutes following the intervention. Blood samples were collected before and 5 minutes following each intervention. Data source: Twenty healthy male smokers were sequentially screened and recruited into the study Population size: 20. Year of data collection: June 2016 and December 2016

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		E-cigarette, smoking and other related status: habitual tobacco smokers of one or more tobacco cigarette per day Intervention and research design: Single-centre prospective randomized crossover study. 20 healthy male smokers were randomized in a crossover fashion to electronic and tobacco cigarette study arms (i.e. Participants were randomly assigned to study arms 'A' or 'B' in a 1:1 ratio). Randomization determined the order that participants received each intervention. Study investigations were performed before and after each intervention. Washout period between study visits was a minimum of 24 h. smokers immediately before and after electronic cigarettes use and tobacco smoking. All participants attended for two study visits at the same time of day, with a minimum of 24 hours between each visit. Outcomes: Heart rate, blood pressure, reactive hyperaemia index (RHI, microvascular reactivity), augmentation index (arterial stiffness) and respiratory function. PWA occluded arm (AU), PWA control arm (AU), augmentation index, exhaled carbon monoxide, FEV1, forced expiratory volume in 1 s; FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity ratio; PEF, peak expiratory flow; PWA, pulse wave amplitude; RHI, reactive hyperaemia index. Heart rate increased after electronic cigarettes use and tobacco smoking, whereas blood pressure remained unchanged. Reactive hyperaemia index, augmentation index (P¼0.010) but not augmentation index standardized to heart 75bpm increased with electronic cigarettes use but not with tobacco smoking. Following tobacco smoking, there was a significant increase in total microparticles (P<0.001), EMPs (P<0.001) and PMPs (P<0.001). In contrast, electronic cigarettes were only associated with an increase in PMPs (P<0.001), with no significant changes in the total microparticle fraction or EMPs (all P>0.05). Peak expiratory flow significantly decreased following electronic cigarettes use. The authors concluded that acute exposure to tobacco smoking as well as to e-cigarettes influences vascular and respiratory function. Where tobacco smoking significantly increased microparticle formation, indicative of possible endothelial injury, e-cigarette use induced vasoreactivity and decreased peak expiratory flow. These findings suggest that both e-cigarette and tobacco smoking negatively impact vascular and respiratory function.[374] Device and product: For the e-cigarette intervention participants were asked to use a commercially available second-generation e-cigarette device with nicotine-containing e-liquid. The device consisted of a 1300mAh variable voltage rechargeable battery, a tank and an atomizer (SmokeMax; Groove Trading Ltd, Glasgow, UK). Each tank contained approximately 1.5 ml of e-liquid. The e-liquid used in the study was reported by the manufacture to contain 18 mg/ml nicotine, and was tobacco flavoured (Pillbox38 UK Ltd, Totally Wicked, Blackburn, UK). All the e-liquid used in the study was manufactured from the same batch. The e-liquid control of substances hazardous to health (COSSH) assessment report from the manufacture stated that the contents per 10 ml bottle were: 360-mg nicotine, 12.6-ml propylene glycol, 6.2-ml vegetable glycerine, 120-mg vanillin, 48mg furaneol and 80-mg ethyl vanillin. An independent analysis of the e-liquid was performed at the Nicotine and Tobacco Product Assessment Shared Resource (NicoTAR), Roswell Park Cancer Institute, Buffalo, New York, USA. Nicotine concentrations were determined using gas chromatography (GC) with a nitrogen–phosphorus detector (GC–NPD). Flavouring compounds were also identified in each liquid using a GC/mass spectrometry method. According to the laboratory report, the average nicotine content was 17.27 mg/ml and the identified flavouring compounds correlated closely with the manufactures COSSH report Each participant was provided with a new e-cigarette device, which was prepared by the study investigator. The investigator filled the tank with e-liquid and set the battery voltage to 3.3 V. When asked to use the e-cigarette participants were asked to take 15 'puffs' of the electronic cigarette. This is

Author(s) year	Possible benefit or harm	Interventional trial papers respiratory diseases
		considered to be comparable with the amount of nicotine obtained from smoking a conventional combustible tobacco cigarette, approximately 0.5mg

Table 82: Interventional trial papers on oral diseases, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers oral diseases
Reuther *et al.*[375]	Benefit	The authors reported on the immediate **effects of e-cigarettes on perfusion in buccal mucosal tissue in non-smokers.**
2016		Age range: 27 to 38 years. Sex: 7 males, 3 females. Country: UK Duration of trial: Two sessions on separate days. Interval not reported. Measures were gathered up to 30 minutes post intervention Data source: Volunteers, members of staff from the oral and maxillofacial department and ward, Non-smokers Population size: 10. Year of data collection: Not reported E-cigarette, smoking and other related status: Not reported Intervention and research design: Crossover design. Each was given 2 electronic cigarettes, one containing plain "e-liquid" (a solution of propylene glycol and vegetable glycerine) as a control, the second containing nicotine (16 mg nicotine/g of e-liquid). A baseline of capillary blood flow to the buccal mucosa was taken with the laser Doppler probe, both before and after 5 minutes of vaping, and this was recorded as "Prevape" and "0 Minute", respectively. After vaping, measurements were repeated at 5-minute intervals for 30 minutes. The volunteers were not told whether the e-cigarette contained nicotine, but both types were used by all volunteers on separate days. Using a laser Doppler, the moorVMS-LDF2, (Moor Instruments Axminster, Devon, UK) the authors analysed the effect of electronic-cigarettes on the flow of buccal mucosal blood, before and immediately after vaping. Outcomes: After vaping for 5 minutes, capillary blood flow was measured in the buccal mucosa at 5-minute intervals using a laser Doppler probe, and the results were expressed as arbitrary perfusion units. There was a wide variation in results and a small but significant rise (p=0.008) as a result of nicotine vaping, but these fell to the same levels as before within 30 minutes The authors concluded that e-cigarettes may influence blood flow to the oral mucosa, although further trials are needed to show whether they improve healing time after operation.[375] Device and product: Each participant was given two electronic cigarettes, one containing plain "e-liquid" (a solution of propylene glycol and vegetable glycerine) as a control, the second containing nicotine (16 mg nicotine/g of e-liquid).
Wadia *et al.*[376]	Harm	The authors reported findings from a pilot study on **gingival response when smokers switched from smoking to vaping.**
2016		Age mean years (SD): Not reported. Sex: Not reported. Country: UK Duration of trial: Two weeks Data source: Established smokers (all staff members at Guy's Hospital) with mild periodontal disease Population size: 18. Year of data collection: Not reported E-cigarette, smoking and other related status: Established smokers

Author(s) year	Possible benefit or harm	Interventional trial papers oral diseases
		Intervention and research design: Measure were taken before and after substituting vaping for smoking tobacco Outcomes: gingival inflammation measures such as bleeding on probing, levels of selected pro-inflammatory cytokines (specifically IL 1β and IL 8) in gingival crevicular fluid, saliva and serum samples The authors concluded that there was a statistically significant increase in gingival inflammation when tobacco smokers switched from smoking to vaping for 2 weeks, but results should be interpreted with extreme caution since this was only a pilot study.[376] Device and product: At visit one, subjects were given a blu PROTM e cigarette kit (Electric Tobacconist®), an extra bottle of blu PRO Tobacco™ e Liquid (Electric Tobacconist) and written instructions. The e Liquid was Classic Tobacco flavoured and contained 18 mg of nicotine (medium strength). The choice of this particular brand of e cigarette was random and there was no commercial sponsorship from the company. The participants agreed to substitute their regular smoking habits with the use of e cigarettes. They were asked to make a note of any cigarette smoking during the two weeks if complete abstinence was unsuccessful.
Papaseit *et al.*[377] 2017	No harm or benefit	The authors reported on findings following the **monitoring of nicotine intake from e-cigarettes**; specifically, the **measurement of parent drug and metabolites in oral fluid and plasma.** Age mean years (SD): 23.9 ± 3.5. Sex: All male. Country: Italy Duration of trial: Two sessions. Two-day interval. Subjects participated as outpatients in two different randomly assigned 2-h experimental sessions, carried out with at least 2 days washout period between them. Each nicotine administration, monitored by the researcher, consisted of 10 puffs with a 30-s interpuff interval. Blood samples were collected just before the first administration (baseline, time –5 minutes), 5 (after the first administration), 15, 30 and 45 minutes and also just before the second administration (time 55 minutes), then immediately after the second administration (65 minutes after the first administration), and then at 75, 90, 105, and 120 minutes. Data source: The subjects were recruited from the surrounding community by word of mouth Population size: 9. Year of data collection: Not reported E-cigarette, smoking and other related status: All subjects were smokers of at least three tobacco cigarettes per day (mean=9 cigarettes, SD=5) and by at least 1 year (mean=7 years, SD=4 years) without serious adverse reactions to nicotine. Neither of them reported to have tried e-cigarette. Intervention and research design: The study design was a dose, randomized, crossover, and controlled trial with nicotine. Subjects participated in two different randomly assigned 2-hour experimental sessions, in which they were given: one dose of 0.8 mg of nicotine followed by another 0.8 mg nicotine dose 60 minutes later, both administered as a second generation e-cigarette (Nhoss®, e-liquid 16 mg/mL nicotine, flavour “blond”, France) or tobacco cigarette (Marlboro®, 0.8 mg nicotine per cigarette, USA). Outcomes: oral fluid and plasma nicotine, cotinine, and trans-3’-hydroxycotinine The authors concluded that the obtained results support the measurement of nicotine and metabolites in oral fluid in the assessment of intake after e-cigarette use and appear to be a suitable alternative to plasma when monitoring nicotine delivery from e-cigarettes for clinical and toxicological trials.[377] Device and product: One dose of 0.8 mg of nicotine followed by another 0.8 mg nicotine dose 60 minutes later, both administered as a second-generation e-

Author(s) year	Possible benefit or harm	Interventional trial papers oral diseases
		cigarette (Nhoss®, e-liquid 16 mg/mL nicotine, flavour "blond", France) or tobacco cigarette (Marlboro®, 0.8 mg nicotine per cigarette, USA)

Table 83: Interventional trial papers on exposure to e-cigarette toxins, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
van Staden *et al.*[378] 2013	Harm, but less harmful than tobacco cigarettes	The authors reported on **carboxyhaemoglobin levels, and on health and lifestyle perceptions in smokers converting from tobacco cigarettes to e-cigarettes.** Age range: 18 to 50 years. Sex: 8 males, 5 females. Country: South Africa Data source: Participant were recruited from 1 Military Hospital, Pretoria. Duration of trial: Two sessions. One, of two, week intervals Population size: 13. Year of data collection: Not reported E-cigarette, smoking and other related status: Smoking 10 - 30 cigarettes per day Intervention and research design: A single group within-subject design. The participants exchanged their cigarettes for the Twisp e-cigarette and were instructed to smoke this exclusively for a period of two weeks. Participants were evaluated at baseline prior to using the Twisp e-cigarette (visit 1) and again after two weeks (visit 2). Outcomes: Carboxyhaemoglobin levels and oxygen saturation, serum cotinine levels, perception of smoking-related symptoms and lifestyle: carboxyhemoglobin levels (%) were significantly reduced after smoking Twisp e-cigarettes for 2 weeks (mean +/- standard deviation (SD) arterial carboxyhemoglobin before 4.66+/-1.99 v. after 2.46+/-1.35; p=0.014 and mean+/-SD venous carboxyhemoglobin before 4.37+/-2.1 v. after 2.50+/-1.23; p=0.018). A decrease in cotinine levels (p=0.001) and an increase in oxygen saturation (p=0.002) were also observed. Most participants perceived improvements in their health and lifestyle parameters. The authors concluded that smoking the Twisp e-cigarette may be a healthier and more acceptable alternative to smoking tobacco cigarettes.[378] Device and product: Twisp e-cigarette
Hajek *et al.*[387] 2015	Not adequate for benefit	The authors reported on the **nicotine intake from e-cigarettes** following initial use and after 4 weeks of regular use. Age mean years (SD) (range): 52 ± 16 (32 to 74). Sex: 1 male, 5 females. Country: UK Duration of trial: Two sessions. Four weeks interval Data source: Adult smokers interested in stopping smoking recruited through advertisements in local newspapers Population size: 6. Year of data collection: Not reported E-cigarette, smoking and other related status: At the beginning of the study, they smoked on average 25 cigarettes/day (SD = 16, range 10–60) and scored 5.7 (SD = 3.2, range 1–9) on Fagerström Test for Nicotine Dependence. During the study, they reported using on average 1.2 EC cartridges per day (SD = 0.7, range 0.7–2.5). Intervention and research design: On the target quit date (Baseline assessment week 1), participants were provided with an e-cigarette and 15 cartridges and instructions on its use, they attended standard withdrawal oriented behavioural support weekly for 4 weeks. Further supplies of cartridges were available at each session as needed. The instructions suggested that smokers usually find their own way of using e-cigarette; that e-cigarette can be puffed on for 5–10 minutes and may require a few more and longer puffs than cigarettes; and that smokers typically

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		use one cartridge per day, but enough cartridges are provided to use up to two per day. All six participants were smoking and using e-cigarette during the week of their second assessment (week 4). One participant reported smoking less than five cigarettes over the previous week; the others smoked more than five cigarettes. At the two PK sessions, a blood sample was taken after which participants were asked to smoke a fully charged e-cigarette ad lib for 5 minutes. Outcomes: e-cigarette pharmacokinetics (plasma nicotine concentrations) data on the two occasions, that is, when the participants were new to EC use (baseline week 1) and after using e-cigarette for 4 weeks. The peak nicotine levels were achieved within 5 minutes of starting the e-cigarette use, which suggests that e-cigarette may provide nicotine via pulmonary absorption. There were large individual differences in nicotine intake. Compared with the PK profile when using e-cigarette for the first time, 4 weeks of practice generated a 24% increase in the peak plasma concentrations and a 79% increase in overall nicotine intake. The authors concluded that first-generation e-cigarettes provide faster nicotine absorption than nicotine replacement products, but to compete successfully with conventional combustible tobacco cigarettes, e-cigarettes may need to provide higher doses of nicotine. Nicotine intake from e-cigarettes can increase with practice, but further trials are needed to confirm this effect.[387] Device and product: Green Smoke EC with cartridges labelled 2.4% nicotine. This was a first-generation "cig-a-like" re-chargeable device. EC were purchased from the manufacturer. The labelling of nicotine content was accurate, and the model had good consistency in nicotine delivery. It delivered 9 mg of nicotine in vapor more than 300 puffs, which was in the middle of the range of the products tested. Cartridges used in this study were tobacco flavoured and contained nicotine dissolved in a mixture of propylene glycol and vegetable glycerol.
McRobbie *et al.*[379] 2015	Harm, but less harmful than tobacco cigarettes	The authors investigated **exposure to carbon monoxide (CO), nicotine (by measuring cotinine in urine), and acrolein (by measuring its primary metabolite, S-(3-hydroxypropyl) mercapturic acid (3-HPMA) in urine) in smokers and e-cigarette users.** Age mean years (SD): 44.8 ± 13.22 EC use only 48.2 ± 12.37 dual users Sex: 8 male (50%) EC use only: male 9 (52.9%) dual users. Country: England, UK. Duration of trial: Five session. One-week interval. Data source: Adult smokers wanting to stop smoking were recruited through advertisements in free London newspapers Population size: 40. Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers Intervention and research design: Exposures in a cohort of 40 smokers before and after 4 weeks of e-cigarette use, both in exclusive e-cigarette users and dual users. On the target quit date, participants were provided with their e-cigarette and received instructions on its use. They were instructed to use e-cigarette ad-lib. Two cartridges per day were supplied initially, with the supply adjusted to actual use later. Participants received standard withdrawal-oriented behavioural support at baseline, target quit date, and at four further weekly sessions. Outcomes: Changes in CO, cotinine, and acrolein (as measured by its primary metabolite, S-(3-hydroxypropyl) mercapturic acid (3-HPMA; other name N-Acetyl-S-(3-hydroxypropyl)-L-cysteine (i.e. (3-HPMA) from baseline to 4 weeks after target quit date. The authors concluded that a significant reduction in carbon monoxide was observed in e-cigarette users and dual users of e-cigarettes and conventional combustible tobacco cigarettes. Cotinine levels also declined, but to a lesser extent

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		at 17% decrease compared to their baseline measure; and dual users at 44% decrease. Mean acrolein (3-HPMA) levels had decreased at 4 weeks, with a 79% decrease in e-cigarette-only users compared to their baseline measure and a 60% decrease in dual users. In dual users, e-cigarette use significantly reduced exposure to carbon monoxide and acrolein because of a reduction in smoke intake. E-cigarettes may reduce harm even in smokers who continue to smoke, but long-term follow-up trials are needed to confirm this.[379] Device and product: Green Smoke e-cigarette (labelled 2.4% nicotine), a first-generation "cig-a-like" device, purchased directly from the manufacturer's website. At the time of the study, the company produced only one model. From a previous study, the model was noted to provide a consistent nicotine content and delivered 9 mg of nicotine in aerosol over 300 puffs which was in the middle range of the products tested. Peak mean plasma nicotine concentration achieved after 5 minutes of ad lib use, after overnight abstinence, was 5.7 ng/mL (15). While many e-cigarettes include propylene glycol only, Green Smoke includes propylene glycol and vegetable glycerine, the latter being the precursor to acrolein. The authors tested aerosol generated from 5 Green Smoke cartridges for acrolein content using a smoking machine. The average acrolein yield in aerosol delivered in 15 puffs was 19.4 ng (SD 1.5).
O'Connell *et al.*[380] 2016	Harm, but less harmful than tobacco cigarettes	The authors reported on **reductions in biomarkers of exposure to harmful or potentially harmful constituents** following partial or complete substitution of cigarettes with e-cigarettes in adult smokers. Age mean years (SD±): 37.8 (11.1). Sex: 68 males 37 females. Country: USA Ethnicity: American Indian/Alaska Native: n=1 Black or African American: n=17 Black or African American: n=1 Indian/Alaska White: n=86 Data source: Potential smokers were recruited from the Lincoln, NE (USA) area using standard advertising methods (i.e., print and radio advertisements) and from a database of subjects who had previously participated in a clinical research study or who had expressed interest in participating in a study Duration of trial: Six days. Randomization and a five-day forced-switch from usual brand conventional combustible cigarettes to: (i) exclusive commercial e-cigarette use; (ii) dual-use of commercial e-cigarettes and the subject's usual cigarette brand; or (iii) discontinued use of all tobacco or nicotine products. All urine voided by each subject was collected in 24-h intervals from 07:30 on Day -1 through 07:30 on Day 1, and from 07:30 on Day 5 through 07:30 on Day 6, and aliquots were prepared from the 24-h collections. Blood samples were collected on Days -1 and 5 in the evening following dinner to assess exposure to CO and nicotine. Population size: Total 105. Exclusive E-Cigarette use groups: Tobacco rechargeable n=15, Cherry rechargeable n=15, Cherry disposable n=15, Dual use groups: Tobacco rechargeable n=15, Cherry rechargeable n=15, Cherry disposable n=15; Nicotine cessation n=15 Year of data collection: Not reported E-cigarette, smoking and other related status: a smoker for at least 12 months and currently smoked an average of 10 or more conventional manufactured tobacco cigarettes per day (any brand, flavour or style); consistent use of their current usual brand style for 14 days prior to check-in; positive urine cotinine at screening (>=500 ng/mL); and exhaled carbon monoxide CO >12 ppm at screening. Intervention and research design: On the morning of Day 1, subjects were randomized into one of six groups (N=15 each): exclusive E-Cigarette use groups: Tobacco rechargeable, Cherry rechargeable, Cherry disposable, Dual use groups: Tobacco rechargeable, Cherry rechargeable, Cherry disposable

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Outcomes: The urine, blood and inhalation biomarkers of tobacco smoke exposures of: Nicotine equivalents measured: included nicotine and five major nicotine metabolites: nicotine gluc; cotinine; cotinine-gluc; trans-3'-hydroxycotinine; and trans-3'-hydroxycotinine-gluc. NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; 1-HOP: 1-hydroxypyrene; 3-HPMA: 3-hydroxypropylmercapturic acid; S-PMA: S-phenylmercapturic acid; MHBMA: Monohydroxy-3-butenyl mercapturic acid; HMPMA: 3-hydroxy-1-ethylpropylmercapturic acid; CEMA: 2-cyanoethylmercapturic acid. Exhaled breath biomarkers Exhaled CO and NO are measures of acute carbon monoxide exposure and nitric oxide synthase activity The authors concluded that the levels of urinary biomarkers in subjects who completely substituted their usual conventional combustible tobacco cigarettes with e-cigarettes were significantly lower (29–95%) after 5 days. Percentage reductions in eight of nine urinary biomarkers of exposure were indistinguishable from smokers who had quit smoking, except for nicotine equivalents, which declined by 25–40%. Dual users who halved self-reported daily cigarette consumption by replacing them with e-cigarettes exhibited reductions (7–38%) in eight of nine urinary biomarkers but had increased (1–20%) nicotine equivalents. Reductions were broadly proportional to the reduced numbers of cigarettes smoked. Dual user urinary nicotine equivalents were slightly higher when compared to other groups (e-cigarette only group and non-user or cessation group), but not statistically significant. After 5 days, blood nicotine biomarker levels were lower in the and non-user or cessation group (75–96%) and exclusive e-cigarette use group (11–83%), with dual users experiencing no significant reductions. All subjects experienced significant decreases in exhaled carbon monoxide; these decreases in the cessation and exclusive use groups ranged from 88–89%, and from 27–32% in dual users. Exhaled fractional nitric oxide concentration in exhaled breath (FeNO) increased in the cessation and exclusive use groups (46% and 63%, respectively), whereas the dual users experienced minimal changes. Overall, smokers who completely or partially substituted conventional combustible tobacco cigarettes with e-cigarettes over 5 days experienced reductions in harmful or potentially harmful constituents.[380] Device and product: Three commercially available closed system bluTM e-cigarette products (manufacturer, Fontem Ventures B.V., The Netherlands) were evaluated during this study: rechargeable tobacco flavour, rechargeable cherry flavour, and disposable cherry flavour. The rechargeable e-cigarettes consist of a battery segment and a cartomizer segment comprising the heating unit and a liquid reservoir which can be separated from the battery for recharging or replaced when the e-liquid is depleted. The disposable e-cigarette was similar in form with the exception that the battery and cartomizer segments are included as a single, non-separable unit. Both units operated at a voltage of 3.7 volts (nominal). The resistance of the heating element was _3 ohms for the disposable unit and about 3.5 ohms for the rechargeable unit. The maximum operating temperature of each unit was dependent on the charge level of the battery, the state of reservoir fluid fill and on the manner of use and was not recorded in this study. All e-cigarette products contained 24 mg/mL (2.4%) USP grade nicotine, USP grade vegetable glycerol (~50% in cherry flavour and ~80% in tobacco flavour), USP grade propylene glycol (~45% in cherry flavour and ~10% in tobacco flavour), distilled water, and flavourings. Each e-cigarette contained ~1mL of e-liquid by volume. Subjects were provided unopened packs of their reported usual brand of conventional combustible tobacco cigarettes for use during the study. Subjects were randomized into one of six groups (N=15 each): Exclusive E-Cigarette Use Groups Group A1 – Tobacco flavour rechargeable bluTM e-cigarette Group A2 – Cherry flavour rechargeable bluTM e-cigarette Group A3 – Cherry flavour disposable bluTM e-cigarette Dual Use Groups

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Group B1 – Tobacco flavour rechargeable bluTM e-cigarette + usual brand combustible tobacco cigarette Group B2 – Cherry flavour rechargeable bluTM e-cigarette + usual brand l brand combustible tobacco cigarette Group B3 – Cherry flavour disposable bluTM e- cigarette + usual brand usual brand combustible tobacco cigarette Cessation Group Group C – Complete tobacco and nicotine product cessation
Poulianiti *et al.*[390] 2016	Equal effect	The authors reported on **acute active and e-cigarette changes on antioxidant responses and subsequent pathologies measuring redox status.** Age mean years (SD): smokers 36.8 (9.9) non-smokers 28.8 (10.5) Sex: 16 males, 14 females. Country: Greece Duration of trial: Three sessions. Seven-day interval. Active smokers underwent a control session consisting of an active tobacco cigarette smoking session and an active e- cigarette smoking session. Blood samples were collected prior to, immediately after, as well as one hour after the smoking sessions. Non-smokers underwent a control session a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Blood samples were collected prior to, immediately after, as well as 1 h after the smoking sessions. Three different experimental sessions that were performed in a random order (separated by a minimum of seven days). Data source: Two groups of healthy adult volunteers. Active smokers. Passive smokers. Population size: 30. Year of data collection: Not reported E-cigarette, smoking and other related status: 15 smokers (more than 15 cigarettes per day) and 15 non-smokers Intervention and research design: A randomized single-blind crossover design Outcomes: Total antioxidant capacity, catalase activity and reduced glutathione The authors concluded that tobacco and e-cigarette smoking exposure do not acutely alter the response of the antioxidant system, under either active or passive smoking conditions. Overall, there is no distinction between tobacco and e-cigarette active and passive smoking effects on specific redox status indices.[390] Device and product: device: GIANT, NOBACCO GP, Greece. The e-cigarette liquid (NOBACCO USA MIX, NOBACCO GP, Greece) used, had tobacco taste and contained 11 mg/ml nicotine
Valentine *et al.*[389] 2016a	Harm	The authors reported on the **effects of alcohol-containing e-cigarettes** on young adult smokers. Age mean years (SD): 25.7 ± 2.7. Sex: 14 males, 6 females. Country: USA Duration of trial: Two sessions. Two-day interval. Test sessions were conducted in the early afternoon and participants were instructed to abstain from alcohol for 48 hours, and from all tobacco and nicotine products for 12 hours, before the sessions. Prior to each test session, an indwelling 20-gauge, flexible catheter was inserted into an antecubital vein for blood sample collection. Each test session consisted of a 5-minute directed puffing session (10 puffs total) followed by two, 20 minutes ad lib sessions separated by 20 minutes. The sessions were conducted at least 48 hours apart to minimize carry over effects. Data source: Not reported Population size: 16. Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers who reported drinking socially, use of an e-cigarette at least once in the past year, and daily or non-daily

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		use of tobacco cigarettes within the past 6 months, were enrolled. All participants reported daily use of cigarettes for the 6 months prior to study entry. Participants smoked for an average of 8.7 (4.3) years and scored 4.6 (2.4) on the Fagerström Test for Nicotine Dependence (FTND) indicating moderate dependence. The median lifetime duration of e-cigarette use was 2 months with a range 0–16 months. Twenty-seven percent of participants reported preferring e-cigarettes, 47% cigarettes, 13% having no preference and 13% that their preference was dependent on the context of use. The cumulative percentage of responses to four different intensity intervals (in number days) of any e-cigarette in the past month was20% no use, 93% 1–10 days, 93% 11–20 days and 100% over 21 days. Intervention and research design: Randomized, double blind, crossover design (randomized, within-subjects, counterbalanced design). Acute changes in subjective drug effects, motor performance and biochemical measures of alcohol and nicotine intake were evaluated after directed and ad lib puffing from two commercially available e-liquids containing nicotine (8 mg/ml), vanilla flavour and either 23.5% (high) or 0.4% (trace) alcohol. Outcomes: Drug Effects Questionnaire, the Biphasic Alcohol Effects Scale and the Purdue Pegboard Dexterity Test (PPDT, Lafayette Instruments, Lafayette, IN) measures two types of motor performance: fine finger dexterity and gross movements of the fingers, hands, and arms. The authors concluded that brief use of a widely available type of e-cigarette containing an e-liquid purchased from an Internet vendor can negatively impact psychomotor performance and, in some instances, produce detectable levels of a urine alcohol metabolite.[193] Device and product: Two commercially available e-liquids containing nicotine (8 mg/ml), vanilla flavour and either 23.5% (high) or 0.4% (trace) alcohol. Type of e-cigarette, the Joyetech eGo-CTM, with a single coil atomizer (2.2 ohms), 2 ml tank, and a 650 milliampere hour battery operating at 3.7 V (6.2 W). To reduce variability in aerosol delivery during test sessions, subjects practiced using the e-cigarette in an adaptation session, inhaling more softly, but for a longer duration (3–4 s) than is customary for a tobacco cigarette. Participants were instructed to notify research staff immediately if any undesirable flavours developed that indicated overheating of the e-liquid (i.e. 'dry puffs'). Subjects were told the purpose of the study was "to measure the effects of alcohol contained in a commercially avail-able e-cigarette refill liquid".
Goniewicz *et al.*[381] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship of **e-cigarettes with a range of carcinogens and toxicants.** Age mean years (SD) (range): 31.0 ± 9.7 (20 to 52). Sex: 60% female Country: Poland. Ethnicity: Caucasian. Duration of trial: Two sessions. Two weeks Data source: Subjects were recruited from the local metropolitan area using advertisements in the media, the internet, posted advertisements in clinics and offices, and by word of mouth. Advertisements used to recruit healthy adult daily smokers referred to the opportunity to reduce cigarette smoking by use of a modified risk tobacco product (MRTP). Population size: 20. Year of data collection: March and June 2011 E-cigarette, smoking and other related status: Subjects smoked an average of 12.1 (7.5) years (range: 4–35); the mean level of nicotine dependence among subjects (as measured by the Fagerstrom Test for Cigarette Dependence [FTCD])39 was 3.9 (2.7) (range: 0–9). At the time of screening, 95% of subjects (n = 19) reported planning to quit smoking, with 80% (n = 16) reporting that they have made at least one quit attempt prior to involvement in the study

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Intervention and research design: Before and after use of the pen-style M201 e-cigarettes Outcomes: Mean Levels of Biomarkers in Smokers (N = 20) at Baseline, after 1 Week and 2 Weeks of Using Electronic Cigarettes. Biomarker urine concentration (Toxicant): Nicotine metabolites: 3-Hydroxycotinine (Nicotine), Cotinine(Nicotine), Nicotine(Nicotine), Cotinine N-Oxide(Nicotine), Nicotine N-Oxide(Nicotine), Norcotinine(Nicotine), Nornicotine(Nicotine), Nicotine equivalents. Nitrosamines (TSNAs): -4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone). Mercapturic acids: 2-hydroxyethylmercapturic acid (Ethylene oxide), 2-Hydroxy-3-buten-1-yl-ylmercapturic acid; (1,3-Butadiene), 3-hydroxy-1-methylpropylmercapturic acid (Crotonaldehyde), 3-hydroxypropyl mercapturic acid (Acrolein), S-phenylmercapturic acid (Benzene), 2-carbamoylethylmercapturic acid (Acrylamide), 2-cyanoethyl mercapturic acid (Acrylonitrile), 2-hydroxypropyl mercapturic acid (Propylene Oxide). Metabolites of polycyclic aromatic hydrocarbons: 1-Hydroxyfluorene (Fluorene), 3-, 4-Hydroxyphenanthrenes (Phenanthrene), 2-Hydroxyfluorene (Fluorene), 1-Hydroxypyrene (Pyrene), 3-Hydroxyfluorene (Fluorene), 2-Hydroxyphenanthrene (Phenanthrene), 1-Hydroxyphenanthrene (Phenanthrene), 2-Naphthol Naphthalene). Toxic gases Carbon monoxide (Carbon monoxide). In total, 45% of participants reported complete abstinence from cigarette smoking at 2 weeks, while 55% reported continued smoking. The authors concluded that the study showed that after switching from tobacco to e-cigarettes, nicotine exposure remains unchanged, while exposure to selected carcinogens and toxicants is substantially reduced. These findings suggest that e-cigarettes may effectively reduce exposure to toxic and carcinogenic substances among smokers who switched to e-cigarette products.[381] Device and product: (M201 Mild, Poland) with 20 tobacco-flavoured cartridges per week containing 11.0 ± 1.5 mg of nicotine in a mixture of propylene glycol and vegetable glycerine (50:50)
Wagener *et al.*[382] 2017	Harm, but less harmful than tobacco cigarettes	The authors reported on the **nicotine delivery profiles and harmful constituent exposures** of second-generation and third-generation **e-cigarette users.** Age mean years (SD): 33.8 ± 10.9. Sex: 60% males. Country: USA Ethnicity: 43% white, 10% black/African-American and 47% multi-race/ethnicity. Data source: Recruited via internet advertisements, flyers and word-of-mouth. Duration of trial: Two sessions. One-week interval. The study design consisted of two phases, a baseline and pharmacokinetic (PK) assessment phase (standardised and ad libitum vaping session). Participation in the baseline phase lasted ∼45 minutes G2 (2nd generation device users) and G3 (3rd generation device users) e-cigarette users attended a second study visit within the next week and were asked to abstain from nicotine containing products 12 hours prior to the visit. Population size: N=30 Smokers n=10, 2nd generation device users n=9, 3rd generation device users n=11 Year of data collection: Not reported E-cigarette, smoking and other related status: Specific eligibility criteria for exclusive e-cigarette users included denying use of any other tobacco/nicotine product ≥3 months and using the same style of e-cigarette device for ≥3 months, and using a G2 device (specified as entry-level tank systems/eGo style tank system without modifications to the tank, atomiser or battery) or a G3 device (specified as an advanced device such as mechanical mods, rebuildable drip tanks, rebuildable atomisers or advanced personal vaporisers). Specific eligibility criteria for smokers

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		included smoking cigarettes ≥3 months and no other tobacco/nicotine product for≥3 months. Intervention and research design: The study design consisted of two phases, a baseline and pharmacokinetic (PK) assessment phase (standardised and ad libitum vaping session. G2 and G3 e-cigarette users attended a second study visit (pharmacokinetic assessment) within the next week and were asked to abstain from nicotine containing products 12 hours prior to the visit. Outcomes: Saliva and urine samples were collected for an analysis of salivary cotinine (metabolite of nicotine) and total urinary NNAL (a metabolite of the lung carcinogen NNK). Exhaled carbon monoxide (eCO; a cardiovascular toxicant) was also assessed. The authors concluded that while baseline cotinine concentration levels among exclusive smokers, second-generation e-cigarette users, and third-generation e-cigarette users are similar (which may have implications for addiction and e-cigarettes' viability as a substitute for smoking), second-generation and third-generation e-cigarette users had significantly lower levels of exposure to a potent lung carcinogen and a cardiovascular toxicant. These findings have significant implications for understanding the addiction potential of these devices and their viability/suitability as aids for smoking cessation. For e-cigarette users, information regarding the nicotine concentration of their e-liquid and specifications of their e-cigarette device (e.g., number of atomiser/heating coils) was also collected. Voltage and resistance metres were used to objectively measure volts and ohms of the e-cigarette device.[382] Device and product: Mean (SD) voltage applied to the atomiser was not significantly different between G2 and G3 devices (G2: 4.1 (0.5) volts vs G3: 4.0 (0.4) volts, p=0.74), but resistance of the atomiser was significantly higher in G2 compared with G3 devices (G2: 2.0 (0.3) Ω vs G3: 0.4 (0.2) Ω, p<0.00001), resulting in significantly higher vaping power in G3 devices (G2: 8.6 (1.9) watts vs G3: 71.6 (50.0) watts, p=0.001). Number of atomiser coils was not significantly different between G2 and G3 devices
Yuki *et al.*[386] 2017	Harm	The authors reported on the **pharmacokinetics of nicotine following the use of a prototype novel tobacco vapour product** in comparison to a conventional combustible tobacco cigarette. Age mean years (range): 39.0 (21 to 63). Sex: All males. Country: Japan Duration of trial: Four days On Day 1, Subjects checked in to the clinic and abstained from their regular tobacco product use. Days 2 and 3 were product use days. On each product use day, subjects used a prototype novel tobacco vapor product or smoked one conventional cigarette under controlled use according to the randomization schedule. The controlled use of both prototype novel tobacco vapor product and conventional cigarette consisted of 10 puffs for 3 minutes at approximately 20-s intervals. On Day 4, subjects were discharged following completion of health assessments. The nicotine yield of the prototype novel tobacco vapor product in 50 puffs, which is the intended puff number of one capsule, was 1.10mg per capsule as measured by the Health Canada machine-smoking test regimen (puff volume: 55 mL, puff duration: 2 s, and puff frequency: 2/min). Blood samples (2 mL) for plasma nicotine analysis were collected via an intravenous catheter inserted into the cutaneous vein of the forearm. Blood was collected at approximately 5 minutes prior to and at 2, 3, 4, 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes after the start of product use on Days 2 or 3. Three additional blood samples were collected following the use of prototype novel tobacco vapor product (at 6, 7, and 8 minutes following the start of prototype novel tobacco vapor product use), with consideration given to a delayed peak concentration of nicotine.

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Data source: Healthy Japanese adult male smokers. Population size: 24 Year of data collection: Not reported E-cigarette, smoking and other related status: Healthy adult male smokers smoking an average of 11 or more manufactured cigarettes per day at screening and had smoked for at least 12 months before entering the trial. Intervention and research design: An open-label, randomized, two period crossover design. Blood was collected at approximately 5 minutes prior to and at 2, 3, 4, 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes after the start of product use on Days 2 or 3. Three additional blood samples were collected following the use of PNTV product (at 6, 7, and 8 minutes following the start of prototype novel tobacco vapor product use), with consideration given to a delayed peak concentration of nicotine. Outcomes: The pharmacokinetic parameters of the maximum observed plasma concentration (Cmax), the time to reach Cmax (tmax), the terminal elimination half-life (t1/2), and the area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUClast) were determined from the nicotine concentrations mouth level exposure, mean plasma nicotine concentration The authors concluded that the results suggest that the prototype novel tobacco vapour product shows a similar pharmacokinetic profile to conventional combustible tobacco cigarettes, while delivering less nicotine following controlled use.[386] Device and product: The prototype novel tobacco Vapor product consisted of a power supply unit, a cartridge with a heater and liquid, and a capsule filled with tobacco blend. The prototype novel tobacco vapor product use product generates a nicotine-free vapor via electrical heating of a liquid, which contains glycerin, propylene glycol and water and does not contain nicotine and flavour unlike major e-liquids for electronic cigarettes. The nicotine yield of the prototype novel tobacco vapor product in 50 puffs, which is the intended puff number of one capsule, was 1.10mg per capsule as measured by the Health Canada machine-smoking test regimen (puff volume: 55 mL, puff duration: 2 s, and puff frequency: 2/min). (conventional cigarette 1:1 mg tar and 0.1 mg nicotine values, measured by ISO machine-smoking (ISO 3308, 2000) and printed on the package. The prototype novel tobacco vapor product differs from most existing “heated tobacco” products in that the tobacco is not directly heated during use. prototype novel tobacco vapor product also differs from many e-cigarettes in that the liquid being vaporized does not contain nicotine. In this study, the pharmacokinetics of nicotine between this novel tobacco product and conventional cigarette smoking were compared. The pharmacokinetic parameters were calculated from the blood nicotine concentrations and the estimated mouth level exposure of nicotine following controlled product use. In this study, the mouth level exposure of nicotine from prototype novel tobacco vapor product use product use was estimated in a different way than the mouth level exposure of nicotine from cigarette smoking.
Czoli *et al.*[383] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the relationship between tobacco and e-cigarette use with a range of biomarkers including carbon monoxide (CO), 1-hydroxypyrene (1-HOP), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Age mean years (SD): 36 (11.7). Sex: 71% male. Country: Canada Duration of trial: Four sessions. Seven-day interval. Participants were asked to attend four laboratory visits: at baseline and one each after a 7-day period Data source: Participants were recruited from September 2015 to March 2016 via advertisements placed in newspapers, online, and in local vape shops, and received $295 for participating in the study Population size: 48. Year of data collection: September 2015 to March 2016

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		E-cigarette, smoking and other related status: Dual users of tobacco cigarettes and e-cigarettes. Dual users were identified as current daily tobacco cigarette smokers (had smoked ≥100 cigarettes in their lifetime and smoked ≥5 cigarettes/day) and current daily e-cigarette users (had used an e-cigarette at least once a day for each of the past 7 days). Intervention and research design: Nonblinded within-subjects crossover experiment. Participants completed three consecutive 7-day periods in which the use of tobacco cigarettes and e-cigarettes was experimentally manipulated, resulting in four study conditions: Dual use, Tobacco cigarette use, E-cigarette use, and No product use Outcomes: Compared to dual use, cotinine remained stable when participants exclusively smoked, but significantly decreased when they exclusively vaped, despite significant increases in e-cigarette consumption. Levels of biomarkers of exposure to toxicants, including carbon monoxide (CO), 1-hydroxypyrene (1-HOP), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). The authors concluded that although dual use may reduce exposure to tobacco smoke constituents to some extent, abstaining from smoking is the most effective way to reduce such exposure. They also stated that public health authorities should clearly communicate the relative risk of e-cigarettes and tobacco cigarettes to the general public, focusing on two salient points: (1) e-cigarettes are not harmless, but they are less harmful than tobacco cigarettes; and (2) using e-cigarettes while smoking may not necessarily reduce health risks; therefore, consumers should stop smoking completely in order to maximise the potential health benefits.[383] Device and products: Not reported
Round *et al.*[384] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the outcome levels of a range of **biomarkers of tobacco exposure after smokers switch to an e-cigarette or nicotine gum.** Age: 21–60 years of age non-menthol; smoker— Vuse Solo original (41.63 ± 11.22) Non-menthol smoker—nicotine gum (40.18 ± 11.44) Menthol smoker— Vuse Solo menthol (42.55 ± 10.87) M smoker—nicotine gum (41.46 ± 10.00) Sex: Non-menthol smoker— Vuse Solo original (27 male 11 female) Non-menthol; smoker—nicotine gum (25 male 14 female) Menthol smoker— Vuse Solo menthol (25 male 15 female) Menthol smoker—nicotine gum (30 male 11 female) Country: USA Ethnicity: Non-menthol smoker—VS original (37 Hispanic 1 Latino Non-Hispanic or Latino); Non-menthol smoker—nicotine gum (39 Hispanic 0 Latino Non-Hispanic or Latino); Menthol smoker—VS menthol (40 Hispanic 0 Latino Non-Hispanic or Latino); Menthol smoker—nicotine gum (40 Hispanic 1 Latino Non-Hispanic or Latino) Data source: Generally healthy males and females Duration of trial: Five days. The authors enrolled smokers to switch to Vuse Solo (VS) Digital Vapor Cigarettes (Original or Menthol) or Nicorette 4 mg nicotine gum (NG) in a controlled setting. Subjects who smoked combustible cigarettes ad libitum for 2 days during a baseline period were then randomized to ad libitum use of either Vuse Solo or nicotine gum for 5 days. Biomarkers of 23 toxicants were measured in 24-hour urine samples and blood collected at baseline and following product switch. Subjects who smoked combustible cigarettes ad libitum for 2 days during a baseline period were then randomized to ad libitum use of either Vuse Solo or nicotine gum for 5 days. Biomarkers of 23 toxicants were measured in 24-hour urine samples and blood collected at baseline and following product switch. Population size: 153. Non-menthol; smoker— Vuse Solo original (N = 38) Non-menthol; smoker—nicotine gum (N = 39) Menthol smoker— Vuse Solo menthol (N = 40) M smoker—nicotine gum (N = 41)

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Year of data collection: Not reported E-cigarette, smoking and other related status: Generally healthy males and females, who reported smoking at least 10 combustible, filtered, menthol or non-menthol cigarettes per day and reported smoking their first cigarette within 30 minutes of waking were included in the study. In addition, potential participants had to be willing to switch from their usual brand (UB) cigarettes to Vuse Solo Original flavour, Vuse Solo Menthol flavour, or NG while in clinic. Potential subjects completed a prescreening telephone interview and one screening visit to assess eligibility within 30 days of study enrollment on Day −3. On Day −3, eligible subjects were enrolled in the study and started a 9-day in-clinic residence. Baseline assessments during smoking of subjects' UB cigarettes occurred for the first 3 days (Day −3 through Day −1). On Day 1, smokers were randomized to one of four cohorts. Smokers of non-menthol cigarettes were randomized to one of two cohorts: • Cohort 1: EC − Vuse Solo Original, or • Cohort 2: NG Smokers of menthol cigarettes were randomized to one of two cohorts: • Cohort 3: EC − Vuse Solo Menthol, or • Cohort 4: NG Post–product switch assessments occurred for 6 days (Day 1 through Day 6). Upon completion of study procedures on Day 6, subjects were discharged from the clinic. The Fagerström Test for Nicotine Dependence and a demographic questionnaire were administered to all potential subjects at the screening visit Intervention and research design: randomized, parallel-group, clinical study Outcomes: Urinary nicotine equivalents, Plasma cotinine at 07:00 pm, Plasma nicotine at 07:00 pm; Biomarkers (toxicant) COHb = carboxyhemoglobin (Carbon monoxide), SPMA = S-phenylmercapturic acid (Benzene), 3-HPMA = 3-hydroxypropyl mercapturic acid (Acrolein), HMPMA = 3-hydroxy-1-methylpropylmercapturic acid (Crotonaldehyde), MHBMA = monohydroxybutyl mercapturic acid (1,3-butadiene), CEMA = 2-cyanoethylmercapturic acid (Acrylonitrile), HEMA = 2-hydroxyethylmercapturic acid (Ethylene oxide), NNAL-T = free plus N-glucuronidated (total) 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)), NNN-T = free plus N-glucuronidated (total) N'-nitrosonornicotine (NNN = N'-nitrosonornicotine), NAT-T = free plus N-glucuronidated (total) N'-nitrosoanatabine (NAT = N'-nitrosoanatabine), NAB-T = free plus N-glucuronidated (total) N'-nitrosoanabasine (NAB = N'-nitrosoanabasine), 1-AN = 1-aminonaphthalene (1-aminonaphthalene), 2-AN = 2-aminonaphthalene (2-aminonaphthalene), 3-ABP = 3-aminobiphenyl (3-aminobiphenyl), 4-ABP = 4-aminobiphenyl (4-aminobiphenyl), o-toluidine (o-toluidine), Naphthalene equivalents (Naphthalene), 3-OH-B[a]P = 3-OH-benzo[a]pyrene (Benzo[a]pyrene), 2-OH-fluorene (Fluorene), 1-OH-pyrene (Pyrene), Acrylamide equivalents (Acrylamide), Thiocyanate (Hydrogen cyanide), Urine mutagenicity (General measure of mutagenic properties of urine) The authors concluded that the results indicate that exposure to toxicants when using Vuse Solo is significantly reduced compared with combustible cigarette smoking, and these reductions are similar to those observed with use of nicotine gum. Although statistically significantly decreased, nicotine exposure is maintained closer to conventional combustible tobacco cigarette smoking with Vuse Solo use compared with nicotine gum use. This research suggests that use of Vuse Solo exposes consumers to fewer and lower levels of smoke toxicants than combustible cigarettes, while still providing nicotine to the consumer.[384] Device and product: VS Digital Vapor Cigarettes were introduced commercially by R.J. Reynolds Vapor Company in March 2013. The product is a first-generation cig-alike product composed of a battery, heating element, microchip, sensor, and a cartridge containing e-liquid composed of propylene glycol, glycerin, nicotine, flavourings, and water. During use, the heating element aerosolizes the liquid in the cartridge and produces a puff of aerosol that contains aerosol-forming excipients (propylene glycol and glycerin) and nicotine. A microchip in the cartridge tracks puffing activation time to prevent depletion of e-liquid. Power wattage is the most

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		informative parameter of an EC with respect to the heating of the e-liquid. The effective power to the VS cartridge is controlled to approximately 3 W during a puff. The two brand styles used in this study include VS Original, a tobacco flavour, and VS Menthol. Both brand styles contain approximately 600 µL of a 4.8% nicotine e-liquid, or approximately 29 mg of nicotine. Nicorette nicotine polacrilex gum (GlaxoSmithKline Consumer Healthcare, LP, Philadelphia, PA) is commercially available in 2 and 4 mg strengths. The 4-mg NG was chosen for use in this study in order to include smokers who typically have higher levels of nicotine exposure. Instructions on the package state: "If you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine gum." The White Ice Mint flavour was provided for use in this study. Subjects received written instructions for use based on the Nicorette gum package label. Nicorette gum was the current market leader among oral nicotine replacement therapies at the time this study was conducted.
Beatrice *et al.*[385] 2019	Harm, but less harmful than tobacco cigarettes	The authors reported on exhaled carbon monoxide **levels in smokers after fully switching to e-cigarettes or to a tobacco heating system.** Age mean years (SD): 49.8. Sex: 40 males. Country: Italy Duration of trial: Six months. Data source: Not reported Population size: 40. Year of data collection: Not reported E-cigarette, smoking and other related status: 40 male smokers unwilling or unable to stop smoking were switched to e-cigarettes or tobacco heating systems for six months Outcomes: nicotine addiction and levels of carbon monoxide Intervention and research design: Observations study with intervention. The authors concluded that reduced levels of percentage carboxyhemoglobin did not significantly differ between the two groups, while the tobacco heating system group had a significantly greater reduction in levels of CO parts per million versus the e-cigarette group. Both e-cigarettes and tobacco heating systems are capable of significantly reducing exhaled carbon monoxide at least in the medium term, hence constituting a viable tobacco harm-reduction approach in smokers who are unwilling or unable to stop smoking.[385] Device and product: The tobacco heating system used in this study consists of a tobacco stick (with processed tobacco made from tobacco powder), a holder (which heats the tobacco by means of an electronically controlled heating blade) and a charger that is used to recharge the holder after each use. THS releases nicotine and other volatile compounds by heating the tobacco rod at temperatures not exceeding 350'C. The e-cigarette used in the study was disposable, with a pre-filled cartridge, a low–medium supply power and nicotine 18mg/ml. A low potential e-cigarette (disposable, pre-filled cartridge, low–medium supply power, nicotine 18mg/ml) or a tobacco heating system (THS) 2.2 (sticks with mean nicotine content of 0.50 mg per stick)
St. Helen *et al.*[388] 2020	Harm	The authors reported on the relationship between **e-cigarette use, conventional combustible tobacco cigarette use, and abstention from smoking with a range of volatile organic compounds** (specifically 10 mercapturic acid metabolites of volatile organic compounds). Age mean years (SD): Sex: 28 males, 8 females. Country: USA. Duration of trial: Two sessions. Two-day interval. Data source: Not reported. Population size: 36. Year of data collection: Not reported E-cigarette, smoking and other related status: E-cigarette users, conventional cigarette users

Author(s) year	Possible benefit or harm	Interventional trial papers exposure to e-cigarette toxins
		Outcomes: A range of volatile organic compounds (2-hydroxypropylmercapturic acid; 3-hydroxypropylmercapturic acid; 2-carbamoylethylmercapturic acid; 2-cyanoethylmercapturic acid; 2-hydroxyethylmercapturic acid (acrylonitrile, vinyl chloride, ethylene oxide); 3-hydroxy-1-methyl-propylmercapturic acid; sum of isomers 1-hydroxy-3-buten-2-yl-mercapturic acid and 2-hydroxy-3-buten-1-yl-mercapturic acid; 4-hydroxy-2-buten-1-yl-mercapturic acid; methylmercapturic acid, and phenylmercapturic acid) Intervention and research design: a crossover study with two days of ad libitum vaping or cigarette-only use and two days of enforced abstention The authors concluded that concentrations of volatile organic compound metabolites were higher during smoking compared with during vaping, except for the methylating agents' metabolite. Metabolites of acrylamide were higher during vaping compared with abstention. The 1,3-butadiene and propylene oxide metabolites were higher in variable-power tank users compared with users of cigalikes. E-cigarettes expose users to lower levels of toxic volatile organic compounds compared with cigarette smoking, supporting their harm-reduction potential among smokers. However, some e-cigarettes expose users to volatile organic compounds such as acrylamide, benzene, and propylene oxide, and may pose health risks to non-smoking users.[388] Device and product: Participants used their usual brands of e-cigarettes and cigarettes, provided by the study. The types of e-cigarettes used by study participants were as follows: cig-a-likes (n=12 participants); fixed-power tanks (n=15), variable-power tanks (n=6) and, pod e-cigarettes (n=3, all JUULs)

Table 84: Interventional trial papers on other outcomes, benefits or harms

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
Norton *et al.*[391] 2014	Harm	The authors reported on how **initial puffing behaviours and subjective responses differ between an electronic nicotine delivery system (ENDS) and conventional combustible tobacco cigarettes.** Age mean years (SD): 45.5 ± 3.5. Sex: 37.5 % males, 62.5 % female. Country: USA Duration of trial: Three lab visits over 5 days. Data source: Participants were recruited via advertising in local newspapers (advertising did not mention the study focused on electronic nicotine delivery system) Population size: 16 compliant with study protocol 30 completed study, results represent findings from16 individuals Year of data collection: February 2011- May 2012 E-cigarette, smoking and other related status: smoked at least 10 cigarettes daily, were not concurrently using other tobacco or nicotine products, had no use of e-cigarette in the last 30 days, reported no intention of quitting smoking within the next 30 days Intervention and research design: Participants were asked to visit the laboratory on 3 separate occasions (Days 1, 2, and 5) over 5 days at consistent times of the day and were asked to abstain from regular cigarettes for 72 hours in favour of electronic nicotine delivery system (Smoke 51 TRIO – 3 piece, First Generation with 11 mg/ml filters).

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		Outcomes: Saliva specimen, a spot urine specimen, and an exhaled breath sample for carbon monoxide (CO) testing The authors concluded that ENDS were smoked more intensively than own-brand cigarettes, but delivered significantly less nicotine and were less satisfying. These findings have implications for the viability of certain ENDS as alternatives to cigarettes.[391] Device and product: The 'cigarette-like' "Smoke 51 TRIO" e-cigarette - 3-piece, First Generation with 11 mg/ml cartridges (Vapor Corp, Miami, FL) was tested in this study, as during the study period it was sold in local shopping mall kiosks. All participants used 11 mg nicotine cartridges with flavour (tobacco, menthol) matched to that of their usual cigarette brand; this concentration was chosen as it was the midpoint of the range offered for this brand at the time. Instructions on e-cigarette use and proper charging were also provided verbally during the lab session and in writing for participant home reference. The regular cigarettes were the usual brand of the participant and were not provided as part of the study protocol
Cravo *et al.*[392] 2016	Harm, but less harmful than tobacco cigarettes	The authors undertook a randomised, parallel group study in order to **evaluate the safety profile of an e-vapour product over 12 weeks.** Age mean years (SD): 34.1 ± 10.6 EVP 35.1 ± 10.6 CC Sex: EVP 168 (54.9%) male 138 (45.1%) female CC 58 (56.9%) male 44 (43.1%) female Country: UK. Duration of trial: 12 weeks. Data source: Not reported Population size: 408. 419 were enrolled onto the study and randomised in a 3:1 ratio to the e-cigarette or conventional cigarette (CC) arm. E-cigarette (N = 306) CC (N = 102). Eleven subjects out of the 419 were excluded prior to any product use. The remaining 408 (full analysis set) used the study product at least once. Of these 408 subjects, twenty in the e-cigarette arm and one in the conventional cigarette arm were withdrawn from the study, leading to a total of 387 subjects (94.9% of the full analysis set) having completed the study Year of data collection: Not reported E-cigarette, smoking and other related status: Intervention and research design: Multi-centred (two) open-label, randomised, parallel group, clinical trial conducted in two centres Outcomes: Primary outcomes (safety) Adverse events (AEs): coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1, 2013. Respiratory, thoracic and mediastinal disorders (Sore Throat, Cough), Nervous system disorders (Headache), Infection and infestation (Nasopharyngitis), Psychiatric disorders (Desire to smoke), General disorders and administration site conditions (Irritability), Metabolism and nutrition disorders (Increased appetite) Vital signs: Sitting systolic and diastolic blood pressure, pulse rate and oral temperature 12-lead electrocardiogram: 10-s strips, after the subject has been resting for at least five minutes: heart rate (60/R-R duration), PR interval, QT interval, QTcB, QTcF, QRS duration Lung function tests: Sitting spirometry to measure forced vital capacity (FVC), forced expiratory flow 25%e75% (FEF25%-75%), peak expiratory flow (PEF) and forced expiratory volume in one second (FEV1). Haematology: White blood cell count (WBC), red blood cell count (RBC), haemoglobin, haematocrit (PCV), mean cell volume (MCV), mean cell haemoglobin

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		(MCH), mean cell haemoglobin concentration (MCHC), platelet count, differential WBC Clinical biochemistry: Blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, chloride, calcium, inorganic phosphate, glucose, urea nitrogen (BUN), total bilirubin, creatinine, total protein, albumin, cholesterol (HDL, LDL, and total) Urinalysis: pH, protein, glucose, ketones, urobilinogen, blood and specific gravity Secondary outcomes Biomarkers of exposure in urine: Amount excreted in 24-h urine (Ae24h) for: nicotine equivalents (NEQs: nicotine, cotinine, nicotine-N-glucuronide, cotinine-Nglucuronide,trans 3'-hydroxycotinine and trans 3'-hydroxycotinine glucuronide); S-PMA; 3-HPMA; propylene glycol; total NNAL (NNAL þ NNAL-glucuronide). Other biomarkers of exposure: Exhaled CO, blood COHb Biomarkers of biological effect: Haemoglobin, PCV, RBC, WBC and cholesterol (LDL, HDL and total) MWS-R scores (MWS-R: revised Minnesota Nicotine Withdrawal Scale): The core total scores (sum of the first nine questions on behaviour) and the extended total scores (sum of all 15 questions) were calculated. Symptoms (e.g. angry, irritable, frustrated, depressed, restless, insomnia) were rated from 0 (none) to 4 (severe). Extended total scores may range from 0 to a maximum of 60. QSU-brief scores: Ten statements such as "I have a desire for a cigarette right now", were rated by a number ranging from 1 (strongly disagree) to 7 (strongly agree). Factor 1 scores (sum of questions 1, 3, 6, 7, and 10 for desire and intention to smoke), Factor 2 scores (sum of questions 2, 4, 5, 8, and 9, for anticipation of relief from negative effects with urgent desire to smoke) and total scores (sum of all questions) were calculated. Total scores may range from 0 to a maximum of 70 Adverse events In the EVP group, 271 subjects (88.6%) reported a total of 1515 AEs, and in the CC group, 80 subjects (78.4%) reported a total of 225 AEs. Vital signs, clinical laboratory parameters and body weight There were no clinically significant findings or changes from baseline in sitting BP, sitting pulse rate, body temperature or 12-lead electrocardiogram parameters at any study visit, with the following exceptions: one subject in the EVP group experienced frequent ventricular ectopic beats from Study Day 28, and several subjects in both groups experienced occurrences of increased heart rate-corrected QT intervals compared with baseline (24 subjects in EVP group and 7 subjects in the CC group had occurrences of increased QTcB > 30 ms and 17 subjects in EVP group and 3 subjects in the CC group had occurrences of increased QTcF > 30 ms). Lung function tests No clinically significant changes from baseline were observed in any lung function test parameter, at any study visit. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and forced expiratory flow 25%e75% (FEF25%-75%) appeared to decrease during the course of the study by a maximum of 2.5, 2.4 and 1.5% in the EVP group, respectively, and by a maximum of 3.2, 3.0 and 5.8% in the CC group. The RMANCOVA analysis indicated that the decrease was more pronounced in the CC group compared with the EVP group for FEV1 at Week 8, and for FEF25%-75% at Week 8 and 12. On the contrary, peak expiratory flow (PEF) appeared to increase during the course of the study by a maximum of 2.5% in the

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		EVP group and a maximum of 3.8% in the CC group. These observed changes in PEF were not different between the two study groups. Biomarkers of biological effect Mean haemoglobin levels appeared to be lower than at baseline during the course of the study by a maximum of 2.9% in the EVP group and 2.1% in the CC group. Mean WBC appeared to be lower than at baseline during the study in the EVP group, by a maximum of 6.6%, whereas in the CC group, no consistent changes were observed. Regarding cholesterol, the mean level of HDL cholesterol remained stable throughout the study in the EVP group, whereas in the CC group, it appeared to decrease during the study by a maximum of 3.5%. From this trial, the authors reported the safety profile of an e-vapour product (2.0% nicotine) in smokers of conventional combustible tobacco cigarettes switching to using an e-vapour product for 12 weeks. During the study, no clinically significant product-related findings were observed in terms of vital signs, electrocardiogram, lung function tests, and standard clinical laboratory parameters. Adverse events reported by e-vapour product subjects were more frequent during the first week after switching to the e-vapour product. The frequency of adverse events reduced thereafter and, out of a total of 1,515 reported adverse events, 495 were judged as being related to nicotine withdrawal symptoms. The most frequently stated adverse events were headache, sore throat, desire to smoke, and cough, reported by 47.4%, 27.8%, 27.5%, and 17.0% of subjects, respectively. Only 6% of adverse events were judged as being probably or definitely related to an e-vapour product. Additional observations in e-vapour product subjects included a decrease in the level of urine nicotine equivalents by up to 33.8%, and decreases in the level of three biomarkers of exposure to toxicants known to be present in tobacco cigarette smokers (benzene, acrolein, and NNK). The decrease in nicotine equivalents coincided with an increase in nicotine withdrawal symptoms, measured by a questionnaire, which subsided after 2 weeks. The data presented here show the potential that e-vapour products may offer smokers looking for an alternative to tobacco cigarettes.[392] Device and product: The EVP prototype used in this study was developed by Fontem Ventures B.V. (Amsterdam, the Netherlands). It consisted of a rechargeable battery (voltage range of 3.0e4.2 V), an atomiser and a capsule (small cartridge) containing e-liquid. The capsules were replaceable, and the battery and atomiser were reusable. The wick consisted in a fiberglass string, and the heating coil was a nichrome resistance wire. The base components of the e-liquids used were propylene glycol (70e75% w/w), glycerol (18e20% w/w) and water (5% w/w). Subjects randomised to the EVP arm could choose between two different e-liquids, which differed solely in their flavour: a menthol-flavoured eliquid with 2.0% nicotine (2.7 mg nicotine/capsule) and a tobacco flavoured e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule). Each capsule was expected to provide 40 to 60 puffs, depending on the user's puffing behaviour. Subjects randomised to the CC arm used their own usual CC brand (representative of the UK market; mean ISO nicotine yield 0.81 mg and mean ISO tar yield 9.2 mg).
Russo et al.[334] 2016	Benefit	The authors reported on the relationship **between e-cigarettes and weight gain.** Age mean years (SD): 44 (12.5). Sex: 63 males, 37 females. Country: Italy Duration of trial: One year. Data source: June 2010 to February 2011 Population size: 300 (at recruitment) 100 at completion Year of data collection: Not reported E-cigarette, smoking and other related status: Outcomes: weight measured (at week-12, week-24 and week-52)

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		Intervention and research design: 12-month, randomized controlled trial of smokers invited to switch to e-cigarettes The authors concluded that smokers who quit smoking by switching to e-cigarettes may limit their post-cessation weight gain, with substantial reversal in weight gain manifesting at later timepoints.[334] Device and product: Categoria" Arbi Group Srl, Italy. EC kits with either "Original 2.4%" cartridges for 12 weeks (Group A), or "Original 2.4%" for 6 weeks and a further 6 weeks with "Categoria 1.8%" (Group B), or "Original 0%" cartridges for 12 weeks(Group C).
Rosbrook *et al.*[394] 2016	Harm or benefit depends on point of view	The authors reported on the **sensory effects of menthol and nicotine in an e-cigarette.** Age range: 18–45 years. Sex: 16 males, 16 females. Country: USA Duration of trial: Two sessions on two separate days. Each session contained several trials, 10 in session 1 and six in session two. There was a 10-minute break between each trial. Measures were assessed during the trials Data source: Participants were paid to participate in each experiment and were recruited by flyers posted around the Yale University campus and online advertisements in the New Haven, Connecticut area Population size: 32. Three females and three males served in both experiments, the remaining 26 participants in the second experiment were new to the study. Year of data collection: Not reported E-cigarette, smoking and other related status: all participants were self-reported menthol cigarette smokers Intervention and research design: Adult cigarette smokers sampled aerosolized E-liquids containing five different concentrations of nicotine with 0%, 0.5%, or 3.5% l-menthol, as well as two commercial menthol flavours with and without nicotine. All testing was done using the V2 Standard E-Cigarette (79 mm; VMR Products, LLC) and V2 blank cartridges. In experiment 1, the blank cartridges were filled with 15 different E-liquids that were prepared by Pace Engineering Concepts, LLC: five concentrations of nicotine (0, 6, 12, 18, 24 mg/ml) with 0.0%, 0.5% or 3.5% l-menthol in a 70% propylene glycol (propylene glycol)/30% vegetable glycerine (VG) base. The decision to use 3.5% menthol was based on preliminary tests which indicated this concentration produced cool/cold sensations approximately equal to those experienced from a mentholated commercial flavour E-liquid (Menthol, AmericanELiquidStore) when inhaled using the V2 E-cigarette. In experiment 2, the blank cartridges were filled with six different E-liquids, also in a 70% propylene glycol /30%VG base: two Menthol and two Menthol–Mint commercial flavours (AmericanELiquidStore) with one of each flavour containing 0 or 24 mg/ml nicotine; and two Unflavoured E-liquids (propylene glycol /VG base only) containing 0 or 24 mg/ml nicotine prepared by Pace Engineering Concepts, LLC. Outcomes :Perceived Irritation/Harshness was unaffected by a low (0.5%) menthol concentration, whereas a high menthol concentration (3.5%) led to higher perceived Irritation/Harshness at low nicotine concentrations but to lower Irritation/Harshness at the highest nicotine concentration (24 mg/ml); (2) a commercial Menthol–Mint flavour produced similar results; (3) nicotine tended to enhance rather than suppress sensations of Coolness/Cold; and (4) menthol tended to slightly increase liking independently of nicotine concentration The authors concluded that the evidence indicated that menthol can potentially improve the appeal of e-cigarettes not only via its coolness and minty flavour, but also by reducing the harshness from high concentrations of nicotine.[394]

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		Device and product: the V2 Standard E-Cigarette (79 mm; VMR Products, LLC) and V2 blank cartridges. In experiment 1, the blank cartridges were filled with 15 different E-liquids that were prepared by Pace Engineering Concepts, LLC: five concentrations of nicotine (0, 6, 12, 18, 24 mg/ml) with 0.0%, 0.5% or 3.5% l-menthol in a 70% propylene glycol/30% vegetable glycerine (VG) base. The decision to use 3.5% menthol was based on preliminary tests which indicated this concentration produced cool/cold sensations approximately equal to those experienced from a mentholated commercial flavour E-liquid (Menthol, AmericanELiquidStore) when inhaled using the V2 E-cigarette. In experiment 2, the blank cartridges were filled with six different E-liquids, also in a 70%PROPYLENE GLYCOL /30%VG base: two Menthol and two Menthol–Mint commercial flavours (AmericanELiquidStore) with one of each flavour containing 0 or 24 mg/ml nicotine; and two Unflavoured E-liquids (PROPYLENE GLYCOL /VG base only) containing 0 or 24 mg/ml nicotine prepared by Pace Engineering Concepts, LLC. For all stimuli 0.5 ml of the E-liquids was carefully pipetted into the blank cartridges. Leakage of the E-liquid onto the heating element inside each cartridge was prevented by inserting a cylindrical wooden toothpick into the core during pipetting. After filling, each cartridge was pre-tested using a syringe to create simulated puffs and was used with only one subject.
Riggare *et al.*[395] 2017	Benefit	The authors investigated the effectiveness of nicotine delivered through e-cigarettes for **managing levodopa-induced dyskinesia, associated with Parkinson's disease, with nicotine.** Age years (SD): 45. Sex: female. Country: Sweden Data source: The first author of the paper was the sole study participant Duration of trial: One session. One hour. Population size:1 Year of data collection: Not reported E-cigarette, smoking and other related status: Outcomes: self-tracking of levodopa- induced dyskinesia with nicotine The authors used the term patient-driven N-of-1 for self-tracking the effect, in this instance **managing levodopa-induced dyskinesia with nicotine**, with the explicit intention to disseminate the results by academic publishing. The authors concluded that nicotine administered via e-cigarettes may have a reducing effect on levodopa-induced dyskinesia in individual patients with Parkinson's disease.[395] Device and product: Two identical sets of e-cigarettes (KangerTech mini starter kit) were purchased together with two bottles of e-juice of identical flavour, one with nicotine (3 mg/ml) and the other without. The subject took additional levodopa (25 mg) an hour before the start of the experiment to increase the likelihood of dyskinesia. The e-cigarettes were used as the therapeutic intervention
Lee *et al.*[396] 2018	Harm	The authors reported on the **effects of second-hand exposure to nicotine from e-cigarettes.** Age mean years (SD): 29.4 (6.0). Sex: 60% males. Country: USA Duration of trial: Two sessions. Two consecutive days. Each session one-hour duration. Data source: Healthy non-smoking adults (fewer than 100 cigarettes in lifetime and no smoking in the past 30 days) without cardiovascular disease and with no current use of any medication recruited from the Harvard T.H. Chan School of Public Health in Boston, MA Population size: 5. Year of data collection: March to May 2015

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		E-cigarette, smoking and other related status: healthy non-smoking volunteers Outcomes: Cardiac autonomic effects of short-term second-hand exposure to nicotine from e-cigarettes emissions, specifically heart rate variability and heart rate–corrected QT interval Intervention and research design: randomized, repeated measures crossover study The authors concluded that there are cardiac autonomic effects of short-term second-hand exposure to nicotine from e-cigarette emissions in healthy non-smokers.[127] Device and product: An automatic multiple smoking machine (Modified TE-2 system, Teaque Enterprises, Davis, CA) was used to provide two standard puffs per minutes. Twenty-five percent of the flow from the smoking machine was diluted using particle free, humidified room air in a mixing tube at an output flow of 120 LPM into a cone, from which the participant breathed the diluted EC vapor in a sitting position with breathing as usual. Dilution ratio (1:370) was calculated to be approximately equivalent to that of an exposure chamber (27 m3) with an air exchange rate of 1 per hour.
Melstrom *et al.*[397] 2018	Harm	The authors reported on the **systemic absorption of nicotine following acute second-hand exposure to e-cigarette aerosol** in a realistic social setting. Age mean years (SD): 28–54 years. Sex: 4 males, 2 females Country: USA. Ethnicity 4 white and 2 African-American Duration of trial: Two sessions. Seven-day interval period. Data source: Not reported Duration of trial: The recruitment period began in February 2015. The first exposure session was conducted on March 19, and the second on March 26, 2015. Population size: 6. Year of data collection: February 2015 to March 2015 E-cigarette, smoking and other related status: Six non-users of nicotine-containing products were exposed to second-hand aerosol from ad libitum e-cigarette use by three e-cigarette users for 2 hours during two separate sessions (disposables, tank-style). All participants were present for both sessions. On each study day, within 2 h prior to the 2-hour exposure, the following were obtained from the non-users: blood, urine, and saliva samples; blood pressure; pulse; expired carbon monoxide and self-reported symptoms. Before and following each exposure, the masses of the e-cigarette products were measured to determine the amount of e-cigarette solution used during the exposure. After each 2-hour exposure, the active users were discharged, and the non-users monitored for an additional 6 h for collection of biological samples. Characteristics of the six non-users were as follows: four male and two females; ages 28–54; four white and two African-American. Three habitual e-cigarette users had a median length of e-cigarette use of 1 year and reported using e-cigarette liquid strength ≥18 mg/ml at a median of 50 puffs/hour. One active user currently used both first generation and tank systems. No active user reported using other tobacco products. Intervention and research design: Pre-exposure (baseline) and post-exposure peak levels (Cmax) of cotinine were measured in non-users' serum, saliva, and urine over a 6-hour follow-up, plus a saliva sample the following morning. Six non-users of nicotine-containing products were exposed to second-hand aerosol from ad libitum e-cigarette use by three e-cigarette users for 2 hours during two separate sessions (disposables, tank-style). Outcomes: Non-users' levels of cotinine in serum, saliva, and urine

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		The authors concluded that although exposures may vary considerably, non-users can systemically absorb nicotine following acute exposure to second-hand e-cigarette aerosol.[397] Device and product: Two separate exposure sessions were undertaken to account for e-cigarettes' market diversity. During the first session, the active users used first generation e-cigarettes and tank-style second generation e-cigarettes during the second. Except for the type of e-cigarette used, both sessions were conducted identically. The amount of nicotine consumed was calculated by converting the mass of solution consumed into volume by dividing the mass of solution by either the specific density of propylene glycol (1.032 g/cm3) or of VG (1.261 g/cm3) or, if the solution was a blend, by estimating it to be a 50:50 ratio and averaging the specific density to 1.147 g/cm3. The volume was multiplied by the measured nicotine concentration to yield mass of nicotine consumed during the exposure. The unused e-cigarette cartridges and solutions were collected and sent to the Centers for Disease Control and Prevention (CDC) for analysis of pH and nicotine concentrations, where the latter analysis was performed in a manner that aligned with the method described in Stanfill et al (Stanfill et al., 2009). Analysis of pH was performed as previously described with minor modifications Using the measured pH values, pKanicotine=8.02 and the Henderson-Hasselbalch equation pH=pKa+log10([Base]/[Acid]), the percentage of nicotine in the unionized, or free-base, form was calculated. Each active user was given an iTaste (Innokin Technology Co. LTD, Shenzen, China PRC) variable voltage v3.0 tank (distributed by Mt Baker Vapor) and several selected blu (blu e-cigarettes, Imperial Tobacco Group, Bristol, UK) or Fling (White Cloud Electronic Cigarettes, Tarpon Springs, Florida) disposable e-cigarettes, based on the user's preferred flavours. The devices were identical to those they would use during the exposure sessions and allowed each active user to become familiar with these products. The blu disposable e-cigarette brand was selected and the flavours offered for both study days were based on their position as most popular according to US market share, using existing retail scanner data at the time of the study. The Fling disposable e-cigarette was added to expand the flavour choices. Given the lack of retail scanner data for tank-style systems, the iTaste was selected as a common brand. No flavour ingredient that has known concerns based on a literature review was used (e.g., known to contain diacetyl). The blu e-cigarettes were purchased at the same time from a local Baltimore tobacco retailer and the Fling e-cigarettes was purchased on-line from an e-cigarette retailer. All e-liquid for the second exposure was purchased from a local Baltimore "vape shop" at the same time as custom manufactured solutions. Flavours selected by the users were blu® classic tobacco and cherry crush, Fling® iced berry and custom manufactured solutions were java, swiss cherry and peach
Walele Tanvir *et al.*[393] 2018	Harm, but less harmful than tobacco cigarettes	The authors reported on the **safety profile of Puritane™, a closed-system e-vapour product**, when used by smokers of conventional combustible tobacco cigarettes in a real-life setting over a 24-month period. Outcome measures included adverse events, vital signs, electrocardiogram, lung function tests, exposure to nicotine and selected smoke constituents, nicotine withdrawal effects, and smoking desire. No serious adverse events related to e-vapour product use were observed. Age mean years (SD): Overall (N=209) 36.6 ± 10.2. Sex: males 115 (55.0%) Country: UK Duration of trial: Twenty-four months. Subjects attended the study centres for assessments at Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24. Measures were assessed at each visit, reflecting levels in samples, or questionnaire information, provided at the visit.

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		Data source: Two-centre ambulatory clinical study with 209 healthy volunteers, participants included subjects who had used an electronic vapour product in a previous study Population size: 209 enrolled and assigned to intervention 102 subjects competed the study Year of data collection: Not reported. E-cigarette, smoking and other related status PRIOR TO ENROLLEMENT: Subjects had to be smokers of 5–30 cigarettes per day for at least one year (self-reported). Intervention and research design: subjects were randomised to use either an EVP prototype (EVP arm) or continue using their usual CC brand (CC arm) Outcomes: Outcome measures included adverse events (adverse events were coded using the Medical Dictionary for Regulatory Activities, version 16.1, 2013), 12-lead electrocardiogram parameters, vital signs, lung function tests and clinical laboratory parameters (clinical chemistry, haematology and urinalysis) exposure to nicotine and selected smoke constituents, nicotine withdrawal effects and smoking desire. Secondary outcomes included the level of selected biomarker of exposure (BoE) in urine (to harmful and potentially harmful constituents [HPHCs] typically found in CC smoke, and for which a biomarker of exposure in urine has been identified), the level of selected biomarkers of biological effect (BoBE) in blood, nicotine withdrawal symptoms and desire to smoke. Adverse events: Throughout the study, 159 (76.1%) subjects reported a total of 971 adverse events. This represented 35 outcomes grouped under 13 categories Nervous system disorders (Headache, Migraine) Infection and infestation (Nasopharyngitis, Influenza, Urinary tract infection, Lower respiratory tract infection, Upper respiratory tract infection, Ear infection, Gastroenteritis, Tooth abscess, Sinusitis) Respiratory, thoracic and mediastinal disorders (Sore throat, Cough, Nasal congestion) Psychiatric disorders (Nicotine dependence*, Insomnia, Anxiety, Restlessness) Gastrointestinal disorders (Toothache, Nausea, Vomiting, Dyspepsia, Abdominal pain, Diarrhoea) Musculoskeletal and connective tissue disorders (Back pain, Musculoskeletal pain, Pain in extremity, Neck pain) General disorders and administration site conditions (Fatigue) Injury, poisoning and procedural complications (Exposure during pregnancy) Surgical and medical procedures (Tooth extraction) Immune system disorders (Seasonal allergy) Metabolism and nutrition disorders (Increased appetite) Reproductive system and breast disorders (Dysmenorrhoea) Investigations (Weight increased) Vital signs, electrocardiogram, clinical laboratory parameters and body weight: Vital signs (Sitting systolic blood pressure, Sitting diastolic blood pressure, Sitting pulse) Electrocardiogram parameters (PR Interval, QRS Duration, QTcB Interval, QTcF Interval) Lung function tests (forced expiratory volume in one second (FVC (L)), forced expiratory flow (FEV1 (L)), FEF25%-75% (L/sec), peak expiratory flow (PEF) Biomarkers of exposure (also biomarkers of effect): nicotine equivalents (NEQ), 3-hydroxypropyl mercapturic acid (3-HPMA; BoE to acrolein), S-phenylmercapturic acid (S-PMA; BoE to benzene), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL; BoE to 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone [NNK]) and propylene glycol excreted in urine in 24 h (Ae24h) Levels of biomarkers of biological effect: Haemoglobin, White blood cells (WBC), HDL cholesterol, LDL cholesterol Minnesota Withdrawal Scale (MWS-R) and Brief Questionnaire of Smoking Urges (QSU-Brief) The authors concluded that few serious adverse events, or withdrawals due to adverse events, occurred during the 24 months of Puritane™ use, none of which were related to use of the e-vaping product. Headache, nasopharyngitis, cough,

Author(s) year	Possible benefit or harm	Interventional trial papers other outcomes
		sore throat, and nicotine dependence (desire to smoke) were the most common adverse events and were more frequently reported early after product switch. No clinically relevant, product-related findings were observed for the other safety parameters, namely vital signs, electrocardiogram, and lung function. Regarding lung function, small, statistically significant decreases from baseline to month 24 in all four spirometry parameters were observed. These decreases were not judged to be clinically significant. In the present study, no group of subjects continuing to smoke tobacco cigarettes was included; therefore, a comparison with lung function evolution in subjects who would have continued smoking tobacco cigarettes is not possible within this study. However, in the study, e-vaping-compliant subjects who did not use more cartomisers but fewer conventional combustible tobacco cigarettes than the whole study population, showed similar or greater declines in lung function parameters than the overall study population, confirming the positive effect of smoking reduction, even if accompanied by e-vaping product use. In this study, no clinically relevant changes were observed in biomarkers of biological effect. The subjects in the study maintained their urine nicotine equivalents to levels within 75% of their baseline levels (including the pre-tobacco cigarette smoking subgroup), which may have been sufficient to prevent further decreases in white blood cells. Regarding haemoglobin (a marker of haematology) and high-density lipoprotein and low-density lipoprotein cholesterol (markers of lipid metabolism), no clear and consistent trends were observed, with no clear differences between the whole study population, e-vaping-compliant subjects, and completers. Body weight remained stable during the 2 years of Puritane™ use. In conclusion, the use of the e-vaping product for up to 2 years in this study appears to be an acceptable alternative for smokers, with the advantage of reducing the exposure to potentially harmful smoke constituents.[393] Device and product: Commercially available Puritane™, representative of a typical closed system electronic vapour product, consists of a lithium-ion rechargeable battery and a replaceable cartomiser comprising of an e-liquid reservoir pre-filled by the manufacturer, a heating element and a mouthpiece. The battery can be recharged at least 100 times, and one single cartomiser provides 300–350 puffs depending on the user's puffing behaviour. The cartomisers contain 1 mL of e-liquid, which is comprised of 67.5–69.0% (w/w) propylene glycol (propylene glycol), 30.0% (w/w) glycerol, 1.6% nicotine (16 mg/g) and 0.54–1.0% (w/w) flavouring. During the study, the eliquid was available in two different flavours: tobacco or menthol.

Appendix 6: Interventional trial papers by adapted Academies of Sciences framework headings for heat not burn products

Table 85 Interventional trial papers on dependence and abuse liability, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability
		Industry-based trials
Roethig *et al.* [401] 2005	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of carbon monoxide, carboxyhaemoglobin, nicotine, and urine mutagenicity (specifically urine nicotine and five of its metabolites** (nicotine-N-glucuronide, cotinine, cotinine-N-glucuronide, trans-3'-hydroxycotinine, and trans-3'-hydroxycotinine-O-glucuronide)) in conventional combustible tobacco cigarette brand users, electrically heated cigarette smoking system users, and low-tar conventional combustible tobacco cigarette users. Age mean (SD): 31 (10) years. Sex: 55 males, 55 females. Country: Nebraska. USA Data source: Male and female subjects smoking between 5 and 25 conventional combustible tobacco cigarettes (Marlboro Lights) daily were recruited from the general population in Lincoln, Nebraska Trial duration: This was a single-centre, open-label, randomized, forced-switching, controlled, parallel-group design study. Volunteers were admitted to the clinical study site (MDS Pharma Services, Lincoln, Neb) for a 2-day pre-randomization phase beginning in the evening of day –3 and remained confined at the clinical site through day 8 Population size: 110 E-cigarette, smoking and other related status: subjects smoking between 5 and 25 conventional combustible tobacco cigarettes Outcomes: Biomarkers of nicotine equivalents, urine mutagenicity, carbon monoxide, carboxyhaemoglobin and analyte (respirable suspended particulates, carbon monoxide) and total volatile organic compounds (not detailed) **The authors concluded that lowering the temperature during tobacco combustion results in a substantial reduction in exposure to the smoke constituents measured**.[401] Device and products: The four cigarette products used in this study were evaluated for tar, nicotine, and CO delivery in mainstream smoke using a standardized method Federal Trade Commission. The first-generation EHCSS1 (Accord first-generation EHCSS series E4) delivered 3 mg tar, 0.2mg nicotine, and 0.7mg CO. EHCSS2 (Oasis first-generation EHCSS series E4) included a charcoal filter and delivered 2 mg tar, 0.2 mg nicotine, and 0.7 mg CO. The conventional combustible tobacco cigarette brand (CC1, Marlboro Lights) delivered 11 mg tar, 0.8 mg nicotine, and 12 mg CO. The low-tar conventional combustible tobacco cigarette (CC2, Marlboro Ultra) delivered 3 mg tar, 0.3 mg nicotine, and 4 mg CO. (MarlboroUltra and Oasis are trademarks of Philip Morris Products SA, Switzerland.
Picavet *et al.* [402] 2016	Equal harm to conventional combustible tobacco cigarettes	The authors reported on the **relationship between use of the THS 2.1 or conventional combustible tobacco cigarettes, and the pharmacokinetics of nicotine,** specifically a range of mean nicotine concentration curves. Age: 23 to 65 years. Sex: Not reported. Country: Northern Ireland, United Kingdom The study was conducted at Celerion GB Ltd. Data source: Subjects were recruited via the clinical site's database and by advertisements. Trial duration: The trial included a 7-day confined study period with data gathered in two consecutive periods. Each period consisted of a 24-hour (at least) nicotine washout period, 1 day of single product use, and 1 day of ad libitum product use. Population size: 28 Data collection period: May 2012 and June 2012

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability
		E-cigarette, smoking and other related status: The subjects have smoked at least 10 commercially available non-menthol conventional combustible tobacco cigarettes per day for the last 4 weeks prior to screening, with a maximum International Organization for Standardization yield of 1 mg nicotine per conventional combustible tobacco cigarettes, as labelled on the cigarette pack. Outcomes: Nicotine concentration curves (below) and measures such as urge to smoke, cough assessment, modified cigarette evaluation questionnaire • AUC0–last = area under the plasma concentration–time curve from time 0 to the last quantifiable concentration • Cmax = maximum observed plasma concentration; • Cpeak = maximum observed plasma concentration • Ctrough = lowest observed plasma concentration during the same sampling interval in which Cpeak was observed • t½ = terminal elimination half-life; • tmax = time to Cmax; • tpeak = time to the maximum observed concentration The authors concluded that **the THS 2.1 effectively delivers nicotine and achieves similar pharmacokinetic profiles as conventional combustible tobacco cigarettes.** The THS 2.1 also reduced the urge to smoke to a similar degree as conventional combustible tobacco cigarettes.[402] Device and products: The Tobacco Heating System THS 2.1, developed by Philip Morris International, has three components, the heatstick, the holder, and the charger. The heatstick has a tobacco plug containing processed tobacco cast leaf, which is covered by a paper wrap. Except for the much shorter length than conventional combustible tobacco cigarettes, the overall appearance of the heatstick is similar to that of a conventional combustible tobacco cigarette. The holder includes a battery, controlling electronics, and the heater element. The heatstick is inserted into the holder and heats the tobacco via an electronically controlled heating blade. The charger recharges the holder. The energy capacity of the holder is sufficient to maintain a product use session for up to 6 minutes.
Yuki *et al.*[386] 2017	Equal effect	The authors reported on **the pharmacokinetics of nicotine following the use of a prototype novel tobacco vapour product in comparison to a conventional combustible tobacco cigarette.** Age mean: 21 to 63 years. Sex: All males Country: Japan Data source: Not reported Trial duration: An open-label, two-sequence, two period, randomized crossover design. On Day 1, Subjects checked in to the clinic and abstained from their regular tobacco product use. Days 2 and 3 were product use days. On each product use day, subjects used a prototype novel tobacco vapor (PNTV) product or smoked one conventional combustible tobacco cigarette under controlled use according to the randomization schedule. The controlled use of both prototype novel tobacco vapour product and conventional combustible tobacco cigarettes consisted of 10 puffs for 3 min at approximately 20-s intervals. On Day 4, subjects were discharged following completion of health assessments. Population size: 24 E-cigarette, smoking and other related status: Persons who smoked an average of 11 or more manufactured cigarettes per day at screening and had smoked for at least 12 months before entering the trial. The usual brand of cigarettes with a mean tar value of 8.8 mg (range: 1e18 mg) and a mean daily cigarette consumption of 18.1 cigarettes.

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability
		Outcomes: Estimation of mouth levels of nicotine exposure, pharmacokinetics, safety (adverse events). The authors concluded that under the conditions of the present study**, the pharmacokinetics of nicotine following prototype novel tobacco vapour product use were not markedly different from those following conventional combustible tobacco cigarette use, while the** prototype novel tobacco vapour product **provided less nicotine following a controlled single use.**[386] **Device and product:** The prototype novel tobacco vapor product consisted of a power supply unit, a cartridge with a heater and liquid, and a capsule filled with tobacco blend. The prototype novel tobacco vapor product generates a nicotine-free vapor via electrical heating of a liquid, which contains glycerine, propylene glycol and water and does not contain nicotine and flavour unlike major e-liquids for electronic cigarettes. The vapor then passes through the tobacco capsule. In doing so, evaporated constituents arising from the tobacco blend, including nicotine and flavours, pass into the vapor, which can then be inhaled by the user. The nicotine yield of the prototype novel tobacco vapor product in 50 puffs, which is the intended puff number of one capsule, was 1.10mg per capsule as measured by the Health Canada machine-smoking test regimen (puff volume: 55 mL, puff duration: 2 s, and puff frequency: 2/min). The conventional combustible tobacco cigarette (CC1: 1 mg tar and 0.1 mg nicotine values, measured by ISO machine-smoking and printed on the package).
		University-based trials
Adriaens *et al.* [1] 2018	Benefit	The authors reported on a 3-day randomised crossover trial, focusing on the **behavioural and experiential effects of the short-term use of the heat-not-burn product IQOS™**, versus an e-cigarette and versus a conventional combustible tobacco cigarette, in current smokers who were novice users of both IQOS™ and of e-cigarettes. The purpose was to investigate the effect of using IQOS™ on exhaled carbon monoxide, **acute cigarette craving, withdrawal symptoms, and subjective positive and negative experiences** after overnight smoking abstinence, compared to using an e-cigarette or a conventional combustible tobacco cigarette, and to investigate which product (the e-cigarette or IQOS™) would be preferred. Age mean (SD) years: 22 (3.09). Sex: 67% male. Country: Belgium. Almost half of the participants were of Belgian nationality (47%) with the remaining being of other nationalities (e.g., Italian, Pakistani, Indian, etc.). Data source: Dutch and English-speaking participants were recruited via various channels around the University of Leuven (through distribution of flyers in University buildings and local newspaper shops, social media). Trial duration: Depending on the enrolments, intake sessions were carried out in group (with a maximum of six participants) or individually, and lasted approximately 30 min. The authors used a crossover, counterbalanced, within-subjects design for the laboratory sessions. Participants came to the lab (individually or in group, with a maximum of three participants) on three consecutive days, each time at the same hour of the day; each session lasted 70 to 80 min and followed the same procedure. Before each laboratory session, participants needed to abstain from smoking for 12 hours. Participants could use one of the three products ad libitum for five minutes outside the building (only one cigarette or heat-stick was allowed). In each session, only one product was used and the order of product use over the days was completely counterbalanced between participants to control for order effects. At fixed times (T1, T2, T3, T4, and T5) participants filled out questionnaires and performed exhaled carbon monoxide measurements Population size: 30. 46 interested individuals signed up for the intake session, of whom 34 completed all sessions. After data collection, another four participants were excluded due to not complying with the critical inclusion criteria

Author(s), year	Possible benefit or harm	Interventional trial papers on dependence and abuse liability
		E-cigarette, smoking and other related status: Individuals recruited had to be a smoker for at least three years, and smoke at least 10 cigarettes per day Outcomes: Physiological Measures: exhaled carbon monoxide measurements. A subjective effect questionnaire was used to assess sociodemographics variables and information on smoking history, mental health status, and tobacco cigarette dependence, using the Fagerström Test for Nicotine Dependence. Outcomes of cigarette craving, withdrawal symptoms and product evaluation and preferences were gathered. Looking at the effects of using the IQOSTM **heat-not-burn** product compared to smoking and vaping, exhaled carbon monoxide levels decreased significantly from Intake to T0, with at T0 average exhaled carbon monoxide levels (about 3 ppm) approaching that of nonsmokers. After five minutes of IQOS™, the increase in the exhaled carbon monoxide levels was 11% (0.3 ppm) of the baseline values (T0 to T1), with a maximum increase of 27% (T0 to T2; 0.8 ppm). Using the IQOS™ resulted in a reduction of 28% (less than smoking but 2% point more than e-cigarettes). The authors **concluded that short-term use of a specific heat-not-burn product, IQOS™, can be effective in momentarily reducing acute conventional combustible tobacco cigarette craving and withdrawal symptoms, while having a minimal impact on exhaled carbon monoxide levels and being slightly more liked by novice users than an e-cigarette**. They stated, however, that this does not guarantee that craving/withdrawal symptom reduction will also be sustained over longer time spans or in cases of repeated use, nor do they provide assurance that these effects are sufficient to lead to smoking reduction or cessation in smokers willing to quit or cut down on conventional combustible tobacco cigarettes.[1] Device and products: Three products were used during the laboratory sessions—a regular tobacco cigarette, an e-cigarette and the IQOS™ **heat-not-burn** tobacco product. The IQOS™ was purchased in an official IQOS-shop in the Netherlands, since **heat-not-burn** products are not available in the Belgian market. Both regular and menthol-flavoured heat-sticks were purchased. The menthol e-liquid and heat-sticks were only destined for regular menthol cigarette smokers; however, because nobody happened to smoke menthol cigarettes, the menthol products were not used in this study. The e-cigarette was an Eleaf iStick Power 5000 mAh battery, fixed at 8 W, with an Aspire Nautilus 2 tank containing a 1.6 Ohm coil. The e-liquid ("Base Aurora") contained 18 mg/mL nicotine, a PG/VG ratio of 70/30, to which either a tobacco flavour ("7 Leaves", 3 vol%) or a menthol flavour ("Mild Winter-Peppermint", 3 vol%) was added.

Table 86 Interventional trial papers on cardiovascular diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		University-based trials
Biondi-Zoccai *et al.* [22] 2019	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **acute effects of a single use of heat-not-burn cigarettes**, electronic vaping cigarettes, and conventional combustible tobacco cigarettes in healthy smokers. Age (SD): 35 (13) years. Sex: 6 males, 14 females. Country: Italy Data source: Healthy subjects who smoked were recruited Trial duration: Four weeks. This was a university-based, randomized, crossover study. A one-week washout from any tobacco product was recommended at study entry and before each experimental cycle, and smoking history (time when smoking had begun) and intensity (i.e. number of daily cigarettes) was self-reported. Participants were randomly allocated to six different cycles of using a single heat-not-burn cigarette, electronic vaping cigarettes, and traditional tobacco combustion cigarettes. Participants eventually used all three products, with an intercycle washout period of 1 week.

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		Population size: 20 Data collection period: 2017 E-cigarette, smoking and other related status: A one-week washout from any tobacco product was recommended at study entry and before each experimental cycle, and smoking history (time when smoking had begun) and intensity (i.e., number of daily cigarettes) was self-reported. Outcomes: Antioxidant status (enzymatic and nonenzymatic antioxidants – specifically levels of vitamin E, a powerful endogenus nonenzymatic antioxidant, and HBA, a measure of H_2O_2 neutralized by cellular enzymes. Platelet activation (two markers: sCD40L and soluble P-selectin). Endothelial dysfunction (flow-mediated dilation, nitric oxide bioavailability, and blood pressure) The **authors concluded that the acute effects of heat-not-burn cigarettes, electronic vaping cigarettes, and conventional combustible tobacco cigarettes are different on several oxidative stress, antioxidant reserve, platelet function, cardiovascular, and satisfaction dimensions, with conventional combustible tobacco cigarettes showing the most detrimental changes in clinically relevant features, thus suggesting that these modified-risk products may indeed prove useful as tools to quit smoking conventional combustible tobacco cigarettes**. [22] Device and products: Tobacco cigarettes from a leading brand (Marlboro Gold; Philip Morris International, Neuchatel, Switzerland) with a mean nicotine content of 0.60 mg per cigarette according to the package label, vaped 9 puffs from a leading tobacco-flavoured. Electronic vaping cigarettes (Blu Pro, Fontem, Netherlands), charged with a nicotine cartridge with a mean nicotine content of 16 mg, equivalent to 250 puffs according to the package label, thus yielding 0.58 mg of nicotine content in 9 puffs. A leading heat-not-burn cigarette (Tobacco Heating System THS2.2 IQOS with Heets; Amber Label, Philip Morris International) having a mean nicotine content of 0.50 mg per stick according to the manufacturer.
		Industry-based trials
Unverdorben *et al.* [403] 2007	Less harmful than conventional combustible tobacco cigarettes	The authors reported on **exercise performance following reduced exposure to conventional combustible tobacco cigarette smoke** and no smoking in adult smokers switching from conventional combustible tobacco cigarettes to an electrically heated cigarette smoking system or smoking abstinence. Age: 35 to 60 years. Sex: All male. Country: Republic of South Africa Data source: Male adult smokers in good general health Trial duration: During the 7 weeks before the start of the clinical conduct, after giving informed consent and passing initial screening including Symptom-Limited Spiroergometry, each subject was familiarised with the research unit and study procedures. Successful candidates underwent two more Symptom-Limited Spiroergometry, 3 to 7 days apart, to assure that the peak oxygen uptake of the second and the third Symptom-Limited Spiroergometry would not differ by 12% or more. Qualified subjects were admitted to the clinical unit within 7 to 21 days after completion of the screening procedures and randomized to 1 of the 6 exposure sequences. The subjects were not allowed to leave the unit for 10 days unless they withdrew from the study. Population size: 18 Trial duration: The study was designed as an open-label, randomized, controlled, three-period, crossover study conducted at a single research center in the Republic of South Africa. E-cigarette, smoking and other related status: Adult smokers in good general health

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		Outcomes: Improve exercise performance assessed by Symptom-Limited Spiroergometry parameters (measures of dyspnea, lung working capacity, oxygen uptake, anaerobic threshold) and bioanalysis (carboxyhaemoglobin) The authors concluded that this study demonstrates that **reduced exposure to conventional combustible tobacco cigarette smoke and not smoking for 3 days translates into improvements in cardiovascular function as detected by symptom-limited spiroergometry.**[403] Device and products: The products used in the study were a conventional combustible tobacco cigarette (tar, 11 mg; nicotine, 0.8 mg; carbon monoxide, 11 mg) and a second-generation electrically heated cigarette smoking system series JLI (tar, 3 mg; nicotine, 0.2 mg; carbon monoxide, 0.4 mg [Federal Trade Commission method]).The EHCSS consists of a cigarette containing a column of standard cigarette tobacco filler, wrapped in a tobacco mat and paper overwrap, which is inserted into a puff-activated lighter. The lighter's 8 blades heat the cigarette only when the smoker takes a puff, thereby avoiding smouldering of the cigarette between puffs. Using this design, the tobacco reaches a peak temperature of approximately 500°C during puffing. This contrasts with the burning cone of a conventional combustible tobacco cigarette, which can reach approximately 900 °C during puffing.
Unverdorben *et al.*[404] 2008	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **prognostic parameters of heart rate (HR) and rate-pressure-product (RPP)** on exercise performance in adult smokers switching from a conventional combustible tobacco cigarette to a potential exposure-reduced electrically heated cigarette smoking system and no smoking. Age: 35 and 60 years of age. Sex: All males. Country: Republic of South Africa Data source: Smokers in good general health Population size: 18 Trial duration: The study was designed as a single-blind (exercise laboratory staff), randomised, controlled, 3-period, crossover study conducted at a single research centre Republic of South Africa. E-cigarette, smoking and other related status: Smokers in good general health, a smoking history of 20 to 40 cigarettes/day for at least 10 years with brand and daily cigarette use stable for at least 3 months prior to enrolment, and a carboxyhaemoglobin concentration of >2.5% at the initial screening visit Outcomes: Cardiovascular measures of heart rate and carbon monoxide • Carboxyhaemoglobin • Resting heart rate • Heart rate maximum • Heart rate 1-minute post exercise, parameters composed from these measures such as: o Chronotropic response: Heart rate max — Heart rate rest o Heart rate recovery: Heart rate max - Heart rate min post o Rate—pressure-product at rest: Heart rate max x systolic blood pressure o Rate—pressure-product maximum: Heart rate max x systolic blood pressure o Rate—pressure-product 1-minute post exercise: Heart rate min post X systolic blood pressure 1 min post o Rate—pressure-product response: RPPmax-rest o Rate—pressure-product recovery: RPPmax-1min post The authors concluded that this study demonstrates that **reduced exposure to tobacco smoke and not smoking for 3 days may translate into improvements in heart rate and rate-pressure-product parameters that are associated with cardiovascular prognosis**. These improvements seem to be more pronounced during no smoking than during the use of the reduced-exposure product, suggesting a dose-dependent trend.[404]

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		Device and products: The products used in the study were conventional test cigarettes (Philip Morris USA, Richmond, VA) whereas for generation of reduced exposure a second-generation electrically heated cigarette smoking system (EHCSS series JLI, Philip Morris USA, Richmond, VA) was used. According to the Federal Trade Commission (FTC) method, the conventional combustible tobacco cigarettes delivered 11 mg of tar, 0.8 mg of nicotine, and 11 mg of carbon monoxide whereas EHCSS delivered 3 mg of tar, 0.2 mg of nicotine, and 0.4 mg of carbon monoxide The EHCSS consists of a cigarette containing a column of standard cigarette tobacco filler, wrapped in a tobacco mat and paper overwrap, which is inserted into an electrical puff-activated lighter. The lighter's 8 blades heat the cigarette only while the smoker takes a puff, thereby avoiding smouldering of the cigarette between puffs. Using this design, the tobacco reaches a peak temperature of approximately 500°C during puffing. This contrasts with the burning cone of a conventional combustible tobacco cigarette, which can reach approximately 900 °C during puffing.
Roethig *et al*[405] 2008	Harm, but less harmful than tobacco cigarettes	Authors reported on **cardiovascular risk factors in adults' smokers switching from conventional tobacco cigarettes to a second-generation electronic heated cigarette smoking system** Age years: 25 to 65 years Sex: males and females. Country: USA Data source: Not reported Duration of trial: 12 months. Population size: 82 Year of data collection: Not reported E-cigarette, smoking and other related status: Smokers of 10 to 40 manufactured, nonmenthol cigarettes with 1 to 7 mg tar as measured by the Federal Trade Commission method daily for at least 10 years. Outcomes: Subjects had three baseline urine and blood biomarker determinations over a 2-week interval in a controlled, confined clinical setting. Examples: nicotine equivalents (urine nicotine), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (total NNAL). Total 1-OHP, 3-hydroxypropylmercapturic acid (3-HPMA), a metabolite of acrolein, 4-aminobiphenyl hemoglobin (4-ABP Hb), Carboxyhemoglobin (COHb), 3-HPMA) and cardiovascular risk factors (haemoglobin, haematocrit, red blood cells, white blood cells, LDL and HDL Cholesterol, Triglycerides, Fibrinogen, hs-CRP, 11-Dehydrothromboxane B2, 8-epi-Prostaglandin F2α, Bilirubin, von Willebrand Factor, Urine Microalbumin) and safety results i.e. adverse events (e.g. headache). To assess changes in exposure to selected cigarette smoke constituents. Intervention and research design: 12-month, randomized, controlled study controlled, forced-switching, open label parallel-group study. Eligible adult smokers were randomly switched to a second-generation electrically heated cigarette smoking system or to a 6-mg tar Federal Trade Commission conventional cigarette in a 2:1 ratio. After randomization, each subject returned to the clinic at 2 weeks and at 1, 2, 3, 4, 5, 6, 9, and 12 months for blood and 24-hour urine sampling in a controlled, confined clinic setting The authors concluded that there was a rapid and sustained reduction in all biomarkers of exposure after switching to the electronic heated cigarette smoking system, with statistically significant reductions from baseline[405] Device and product: Second-generation electronic heated cigarette smoking system
Munjal *et al.* [406] 2009	Harm, but Less harmful than conventional combustible	The authors reported on the **tone of the autonomic nervous system as reflected by heart rate variability** among users of different tobacco products. Age: 35 to 60 years. Mean age + SD; 42.8 +5.7 years. Sex: All males. Country: Not reported Data source: Male smokers without any evidence of cardiovascular disease were enrolled within 28 days of the screening period Population size: In all, 34 male adult smokers were enrolled in the study, and 30 participants (88.2%) completed the study

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
	tobacco cigarettes	Trial duration: A prospective randomized, controlled, 3-period, crossover study design conducted over three days. For each exposure sequence, the first period was initiated from 4:00 PM to 5:30 PM on day 1 (hour 0) and 72 hours of smoking/no-smoking was allowed. Each day, participants in a smoking group could smoke up to 30 cigarettes at specified smoking opportunities offered at equal intervals (every 32 minutes) from 7:00 AM to 10:59 PM. Smoking was not allowed overnight from 11:00 PM to 6:59 AM. E-cigarette, smoking and other related status: Participants smoked between 20 and 40 non-menthol cigarettes per day for at least 10 years. Outcomes: Heart rate variability derived from the 24-hour electrocardiogram. Specifically, • NN interval: normal-to-normal heart beat interval • SDNN: Standard deviation of all NN intervals • SDANN: Standard deviation of all 5-minute averaged • NN intervals in a 24-hour period • RMSSD: The square root of the mean of all squared differences between adjacent NN intervals in 24-hour period • SDNNI: Mean of the standard deviations of the NN intervals calculated from all 5-minute segments in a 24-hour period • PNN50: Percentage (P) of all NN intervals that differ by 50 milliseconds of all NN (%) • HRVTI: Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7 8125 ms (1/128 seconds) • Heart Rate: Average beats per minute during ambulatory period The authors concluded that **adult smokers tend to show increased heart rate variability with reduced exposure to conventional combustible tobacco cigarette smoke after 3 days, indicating a physiologically favourable change in the autonomous nervous system**.[406] Device and products: The products used in the study were a conventional combustible tobacco cigarette; tar: 11 mg, nicotine: 0.8 mg, carbon monoxide: 11 mg; according to the Federal Trade Commission method) and a potential reduced-exposure product, the third-generation, electrically heated cigarette smoking system (EHCSS series K; tar: 5mg, nicotine: 0.3mg, carbon monoxide: 0.45mg).This device serves solely as a research tool for the development of various risk related assays since it reproducibly reduces exposure to tobacco constituents in humans. The EHCSS consists of a cigarette containing a column of standard cigarette tobacco filler, wrapped in a tobacco mat and paper overwrap, which is inserted into an electronic cigarette lighter. The lighter's 8 blades heat the cigarette only when the smoker takes a puff, thereby avoiding smoldering of the cigarette between puffs. Using this design, the tobacco reaches a peak temperature of approximately 500'C during puffing. This is in contrast to the burning cone of a lit end cigarette, which can reach approximately 900'C during puffing.
Martin Leroy *et al.* [407] 2012	Equal harm to conventional combustible tobacco cigarettes in some measures Harm, but Less harmful than	The authors reported on **biomarkers associated with cardiovascular risk and biomarkers of exposure to 10 selected harmful and potentially harmful constituents** in conventional combustible tobacco cigarette smoke, comparing findings in conventional combustible tobacco cigarette smokers with those smoking the EHCSS series-K cigarette, the EHCSS-K6. Age: 30 to 60 years. Sex: 161 males, 155 females. Country: Poland Data source: Not reported Trial duration: This was a randomised, open-label, controlled study with two study groups, EHCSS-K6 and conventional combustible tobacco cigarettes. The study schedule consisted of eight main study visits, screening (Visit 1), two baseline, weekly assessments (Visits 2 and 3), and five post-randomization weekly assessments (Visits 4–8). The whole study duration was approximately 8 weeks, with the investigational period defined as 5 weeks from the date of randomization (Visit 3/ Day 0) to the last study visit (Visit 8/Day 35). The

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
	conventional combustible tobacco cigarettes for other measures	assessment schedule of biomarkers over the course of the study consisted of blood sampling (in fasted state) on Visits 2, 3, 5, 7, and 8, and a 24-hour urine collection prior to Visits 3 and 8 (for urinary biomarkers). Carbon monoxide breath testing was performed at all visits from Visit 2 through Visit 8. Population size: A total of 338 subjects were enrolled in the study and 316 were randomised. The study was completed by 309 subjects, with 234 and 75 subjects for the EHCSS-K6 and conventional combustible tobacco cigarette groups, respectively. There were 7 subjects who did not complete the study. In the EHCSS-K6 group, 2 subjects were withdrawn as they did not attend study visits and 1 subject withdrew consent. In the conventional combustible tobacco cigarette group, 2 subjects were withdrawn as they did not attend study visits, 1 subject was withdrawn due to influenza and 1 subject for violation of selection criteria Data collection period: The study was conducted in two sessions between October 2007 and April 2008 E-cigarette, smoking and other related status: Subjects were current smokers of commercially available, non-mentholated conventional combustible tobacco cigarettes with a 3–10 mg tar yield with a smoking history of at least 10 years prior to screening Outcomes: Biomarkers and selected harmful and potentially harmful constituents: • White blood cell (WBC) count • WBC differential • Platelet count • Red blood cell (RBC) count • Haemoglobin • Haematocrit • High-sensitivity C-reactive protein (hs-CRP) • Interleukin-6 (IL-6) • Oxidized low-density lipoprotein (oxLDL cholesterol) • Myeloperoxidase • Homocysteine • High-density lipoprotein (HDL) • Low-density lipoprotein (LDL) • Total cholesterol • von Willebrand factor (vWF) • Fibrinogen • Adenosine diphosphate (ADP)-induced platelet aggregation • 8-epi-prostaglandin F2a (8-epi-PGF2a) • 11-dehydro-thromboxane B2 (11-DTXB2) Selected harmful and potentially harmful constituents: • 1,3-Butadiene (Monohydroxybutenyl mercapturic acid (MHBMA)) • 2-Naphthylamine (2-Naphthylamine (2-NA)) • 4-Aminobiphenyl (4-Aminobiphenyl (4-ABP)) • Acrolein (3-Hydroxypropyl mercapturic acid (3-HPMA)) • Benzene (S-Phenyl mercapturic acid (S-PMA)) • Carbon monoxide (Carboxyhemoglobin (COHb)) • Nicotine (Nicotine equivalents (NEq)) • NNK (Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL))

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		• Pyrene (Total 1-hydroxypyrene (total 1-OHP)) • o-Toluidine (o-Toluidine (o-TOL)) The authors concluded that there were no statistically significant differences in the two primary biomarkers between the study groups at the end of the study. End-of-study comparisons of secondary biomarkers between study groups indicated an increase in high-density lipoprotein (HDL) cholesterol, and reductions in red blood cell count, haemoglobin, and haematocrit levels in the EHCSS-K6 group. **All biomarkers of exposure to the selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke were decreased in the EHCSS-K6 group, despite an increase in cigarette consumption, compared to the levels found in the conventional combustible tobacco cigarette group.** There were no apparent differences in any of the safety assessment parameters between the groups, and the overall incidence of study-related adverse events was low.[407] Device and products: The electrically heated cigarette smoking system series-K cigarette was analysed for tar, nicotine and carbon monoxide mainstream smoke yields according to International Organization for Standardization methods. All study cigarettes were conditioned according to International Organization for Standardization standard 3402. Mainstream smoke from electrically heated cigarette smoking system series-K cigarettes was generated on a modified smoking machine with a carousel adapted to use the electrically heated cigarette smoking system series-K cigarette EHCSS series-K lighter. The EHCSS smoke generation conformed with International Organization for Standardization standard; however, some slight technical deviations were required. Tar, nicotine and carbon monoxide were determined according to International Organization for Standardization standards 4387, 10315, and 8454, respectively (International Organization for Standardization, 2000b, 2000c; International Organization for Standardization, 1995). The International Organization for Standardization yields as declared on the electrically heated cigarette smoking system series-K cigarette EHCSS-K6 pack were as follows: 5 mg tar, 0.3 mg nicotine, and 1.0 mg carbon monoxide. As electrically heated cigarette smoking system series-K cigarette EHCSS-K6 cigarettes were not commercially available on the Polish market they were provided free-of-charge to the subjects. Conventional combustible tobacco cigarettes were not analysed or provided to subjects in the conventional combustible tobacco cigarette group, and were purchased by the subjects according to their usual habits
Ogden *et al.* [408] 2015	Equal harm to conventional combustible tobacco cigarettes	The authors reported on changes in **biomarkers of biological effect among adult conventional combustible tobacco cigarette smokers who switched to tobacco-heating systems, snus, or ultra-low machine yield tobacco-burning cigarettes for 24 weeks**. Comparisons were made between smokers and a group of never-smokers at baseline, and among the three tobacco-using groups over time and in comparison with each other. Age: Adults. Sex: Not reported. Country: USA Data source: Not reported Trial duration: This was a randomized, multi-centre study of adult cigarette smokers randomly assigned to switch to a tobacco-heating system (Eclipse brand cigarette, non-menthol and menthol varieties, depending on subject preference), snus (Camel SNUS, subject choice of Frost, Spice and Mellow varieties) or an ultra-low machine yield tobacco-burning cigarette (5 mg Cambridge Filter Method ‘‘tar’’; Camel or Salem, non-menthol and menthol, respectively, depending on subject preference). A fourth group of never smokers was included for baseline (week 0) comparisons. Subjects’ experience with the randomised products was followed for 24 weeks at five clinical research units in the USA managed by Covance Early Clinical Development Population size: 150 (50 per group) E-cigarette, smoking and other related status: Adult cigarette smokers

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		Outcomes: Biomarkers of the following biological effects inflammation/oxidative damage, lipids, hypercoagulable state, Insulin resistance, endothelial function and DNA damage specifically • Isoprostane • Isomers and metabolites (e.g.iPF2a-III, 2,3-dinoriPF2a- III, iPF2a-VI, 8,12-isoiPF2a- VI, and PGF2a) • Soluble intercellular adhesion molecule 1 • C-reactive protein • White blood cells • Fibrinogen • Homocysteine • Haematocrit • Haemoglobin • Platelets • Haemoglobin A1c • High density • lipoprotein • Low density • lipoprotein • HDL/LDL • Oxidized LDL • Triglycerides • Circulating endothelial precursor cells • Sister chromatid exchange The authors concluded that **half of the biomarkers of biological effect evaluated were statistically significantly different in the baseline comparisons between smokers and never-smokers. Differences in C-reactive proteins, high-density lipoproteins (HDL), low-density lipoproteins (LDL), HDL/LDL, triglycerides, fibrinogen, and platelets between smokers and non-smokers, were not observed in this study.** However, such differences have been noted previously in some but not all studies examining these relationships. They noted that consistent and statistically significant differences in pairwise comparisons between product groups were not observed.[408] Device and products: A tobacco-heating system (Eclipse brand cigarette, non-menthol and menthol varieties, depending on subject preference), snus (Camel SNUS, subject choice of Frost, Spice and Mellow varieties) or an ultra-low machine yield tobacco-burning cigarette (5 mg Cambridge Filter Method ‘‘tar’’; Camel or Salem, non-menthol and menthol, respectively, depending on subject preference).
Lüdicke *et al.* [409] 2018a	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on the **risk profile of a new tobacco product**, the menthol THS 2.2, an alternative to conventional combustible tobacco cigarettes. Age:23 to 65 (inclusion criteria). Sex: Not reported. Country: Japan Ethnicity: Japanese Data source: Not reported Trial duration: The study comprised a 4-week screening period (Days −30 to −3), an 8-day confinement period (Days −2 to Day 6), an 85-day ambulatory period (Days 6 to 91), and a 28-day safety follow-up period. Population size: A total of 670 individuals were screened at two study sites, of which 231 tried the menthol Tobacco Heating System (THS 2.2) and 216 were enrolled and randomised. Of these, one subject was discontinued for meeting an exclusion criterion and

Author(s), year	Possible benefit or harm	Interventional trial papers on cardiovascular diseases
		55 were discontinued following the closure of one of the two study sites due to non-compliance with sample collection and data recording procedures. One-hundred and sixty participants were randomised to the menthol Tobacco Heating System (n=78), conventional combustible tobacco cigarettes (n=42), and smoking abstinence (n=40) groups. Data analysis was carried out on 104 study participants. Data collection period: The study was conducted and completed between August 2013 and July 2014 at the Tokyo Heart Center Osaki Hospital, Tokyo, Japan E-cigarette, smoking and other related status: Smoked ≥10 menthol conventional combustible tobacco cigarettes per day with a maximum International Organization for Standardization yield of 1 mg for the previous 4 weeks (self-reported) and had smoked for ≥3 consecutive years. No plan to quit smoking in the next 3 months. Outcomes: The following clinically relevant risk markers were measured: • Oxidative stress—8-epi-PGF2α; platelet activity—11-DTX-B2; • Endothelial function—soluble intracellular adhesion molecule-1 (sICAM-1); • Lipid metabolism—HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and total cholesterol; inflammation—total WBC; • Cardiovascular risk/function—homocysteine, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, • Systolic blood pressure, and diastolic blood pressure; and • Metabolic syndrome—blood glucose, hemoglobin A1c (HbA1c), body weight, and waist circumference. The authors **concluded that switching from conventional combustible tobacco cigarettes to the menthol THS 2.2 was associated with reductions in biomarkers of exposure to conventional combustible tobacco cigarette smoke, and changes were observed in clinically relevant biomarkers of oxidative stress (8-epi-prostaglandin F2α), platelet activity (11-dehydro-thromboxane B2), endothelial function (soluble intracellular adhesion molecule-1), lipid metabolism (high-density lipoprotein (HDL) cholesterol), and lung function (forced expiratory volume in 1 second) which were similar to the smoking abstinent group**. The results suggest that switching to the menthol THS 2.2 has the potential to reduce the adverse health effects of using conventional combustible tobacco cigarettes.[409] Device and products: The menthol Tobacco Heating System (2.62 mg/stick menthol, 1.21 mg/stick nicotine and 3.94 mg/stick of glycerine used as aerosol former, obtained under Health Canada Intense smoking regimen, maximum heating temperature 350 °C) was used in this study. Reference products were menthol conventional combustible tobacco cigarettes of the participants' preferred commercially available brand.

Table 87 Interventional trial papers on respiratory diseases, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases
		Industry-based trials
Unverdorben *et al.*[410] 2010	Harm, but Less harmful than conventiona	The authors reported on the extent and potential **reversibility of changes in pulmonary function** in adult smokers of conventional combustible tobacco cigarettes after 3 days of smoking conventional combustible tobacco cigarettes, or the potential reduced exposure following use of an electrically heated cigarette smoking system, or smoking abstinence.

Author(s), year	Possible benefit or harm	Interventional trial papers on respiratory diseases
	l combustible tobacco cigarettes	Age: 35–60 years. Sex: Males. Country: Republic of South Africa Data source: Not reported Trial duration: The pilot study was designed as a single-blind (technicians and laboratory staff), randomized, controlled, three-period, crossover study conducted at a single research centre. Republic of South Africa. The subjects were not allowed to leave the unit for 10 days unless they withdrew from the study. Data collection timepoint are not clearly reported Population size: 49 E-cigarette, smoking and other related status: Male smokers in good general health without any history or clinical signs of pulmonary disease were recruited through the database of volunteers at the clinical research unit to evaluate cigarette smoking related influences on pulmonary function Outcomes: The parameters measured or computed by the spiroergometry system specifically: • Airways resistance (measured by sGaw Specific conductance (1/cmH2O x s, Gaw conductance (1/cmH2O x s, sRaw Specific resistance (cmH2O x s, Raw resistance (cmH2O x s) • Spirometry (measured by FEV1 Forced expiratory volume after one second (L), FEF 25% Forced expiratory flow after the first 25% of the vital capacity (L/s), FEF 50% Forced expiratory flow after the first 50% of the vital capacity (L/s), FEF 25–75% Forced mid expiratory flow (L/s), PEF Peak expiratory flow (L/s), PIF Peak inspiratory flow (L/s)) • Lung volumes (Vital capacity (L), Forced inspiratory vital capacity (L), Thoracic gas volume (L)) The **authors concluded that the data indicated acute and reversible effects of different cigarette smoke exposures and no smoking on mid- to small-size pulmonary airways in a dose-dependent manner.**[410] Device and products: The products used in the study were conventional combustible tobacco cigarettes (Philip Morris USA, Richmond, VA, USA) and as a potential reduced-exposure product the third generation electrically heated cigarette smoking system (EHCSS series K, Philip Morris USA, Richmond, VA, USA). According to the Federal Trade Commission method, the conventional combustible tobacco cigarettes delivered 11 mg tar, 0.8 mg nicotine, and 11 mg carbon monoxide while EHCSS delivered 5 mg tar, 0.3 mg nicotine, and 0.45 mg carbon monoxide. The EHCSS has been shown to reliably reduce the delivery of selected smoke constituents and smokers' exposure to particulate and gas-phase smoke constituents by 40–95% compared to conventional combustible tobacco cigarettes, and was therefore used as the reduced exposure product. The EHCSS is not intended to be marketed. EHCSS consists of a cigarette containing a column of standard cigarette tobacco filler, wrapped in a tobacco mat and paper overwrap, which is inserted into a Puff Activated Lighter™. One of the lighter's eight blades at a time heats the cigarette only while the smoker takes a puff, thereby avoiding smouldering of the cigarette between puffs. Using this design, the tobacco reaches a peak temperature of approximately 500 °C during puffing This contrasts with the burning cone of a conventional combustible tobacco cigarette, which reaches approximately 900 °C during puffing.

Table 88 Interventional trial papers on exposure to heat-not-burn toxins, benefits or harms

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		Industry-based trials

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		Electrically heated cigarette smoking system
Tricker *et al.* [412] 2012a	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to nine selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke** (Marlboro cigarettes containing 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide (CO)) and levels of urinary excretion of mutagenic material in smokers and in users of one of two EHCSS series-K cigarettes, the EHCSS-K3 cigarette or the EHCSS-K6 cigarette. Age: 19–50 years of age. Sex: 88 males, 87 females. Country: United Kingdom Data source: Subjects normally smoking the Marlboro non-menthol cigarette (M6UK) were randomized into one of the five groups Population size: 175. 160 subjects completed the trial Trial duration: All recruited subjects (N = 175, 88 males and 87 females) completed a 7-day diary prior to check-in on Day -2. All subjects were confined to the clinic from Day -2 to Day 9 under medical supervision. Vital signs were measured, and a physical examination performed. On Day -1, vital signs and a 12-lead ECG were measured, and blood samples drawn for clinical laboratory tests. On Day 0 (baseline), assessments included determination of biomarkers of exposure in a 24-h urine sample, vital signs, carbon monoxide carboxyhemoglobin 17:00, and plasma cotinine. One hundred and sixty subjects (80 males and 80 females) were randomised into 1 of 5 parallel groups (EHCSS-K3, EHCSS-K6, M6UK, and PM1 cigarettes, and no-smoking; N = 32 subjects per group). From Day 1 through Day 8, subjects participated in their assigned study groups. Assessments included determination of biomarkers of exposure in 24-h urine samples, vital signs, and determination of carbon monoxide carboxyhemoglobin 17:00 and COT-P17:00. On Day 9 (end of study), vital signs, ECG, clinical laboratory tests, and a physical examination were performed. On Day -2 through Day 0, subjects were only permitted to smoke the M6UK cigarette, on Day 1 through Day 8 subjects smoked their randomized study cigarette or stopped smoking if they were randomized to the no-smoking group. M6UK and PM1 cigarettes were lit using a blue flame gas lighter. EHCSS-K3 and EHCSS-K6 cigarettes were smoked using the EHCSS heater. To ensure study integrity, all M6UK and PM1 cigarette butts and smoked EHCSS-K3 and EHCSS-K6 cigarettes were collected. E-cigarette, smoking and other related status: Adult male and female smokers with acceptable health conditions who had smoked 10–25 cigarettes per day and the Marlboro non-menthol cigarette (6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide) as their exclusive brand for at least 4 weeks prior to screening were recruited Outcomes: selected harmful and potentially harmful constituents in cigarette smoke and excretion of mutagenic material in urine • 1,3-Butadiene Monohydroxybutenyl mercapturic acid (MHBMA) • Acrolein 3-Hydroxypropyl mercapturic acid (3-HPMA) • Benzene S-Phenyl mercapturic acid (S-PMA) • Carbon monoxide Carboxyhemoglobin (COHb) • Crotonaldehyde 3-Hydroxy-1-methylpropyl mercapturic acid (3-HMPMA) • Nicotine Cotinine (COT-P) • Nicotine equivalents (NEq)c • NNKb Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) • Pyrene Total 1-hydroxypyrene (1-OHP)e • o-Toluidine o-Toluidine (o-TOL) • Mutagens Salmonella mutagenicity (YG1024 with S9) The authors **concluded that the study showed strong mean reductions in uptake of selected harmful and potentially harmful constituents in cigarette smoke, and reductions**

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		in excretion of mutagenic material in urine, from baseline to day 8 in M6UK non-menthol cigarette smokers who switched to smoking either the EHCSS-K3 or the EHCSS-K6 non-menthol cigarettes. Smokers who switched to smoking PM1, a conventional combustible tobacco non-menthol cigarette representative of the low-tar cigarette market, showed smaller reductions. The largest mean reductions occurred in smokers who stopped smoking.[412] Device and products: Conventional combustible tobacco cigarette brands were selected to include a leading market share cigarette of similar International Organization for Standardization tar and nicotine yields to the EHCSS-K6 and a representative conventional combustible tobacco cigarette with a low ISO tar and nicotine yield. The cigarettes also had a similar tobacco blend to that used in the EHCSS test cigarettes. Study cigarettes were analysed for tar and nicotine according to ISO methods. All study cigarettes were conditioned according to ISO standard 3402 (International Organization for Standardization, 1991). Conventional combustible tobacco cigarettes were smoked on a smoking machine according to ISO standard 3308 (International Organization for Standardization, 2000a). Tar, nicotine and CO were determined according to ISO standards 4387, 10315, and 8454. Mainstream smoke from EHCSS cigarettes was generated on a modified smoking machine with a carousel adapted to use the EHCSS series-K lighter. The EHCSS smoke generation conformed to ISO standard 3308; some slight technical deviations were required. The ISO yields as declared on the cigarette packaging were as follows: Marlboro (M6UK; 6 mg tar, 0.5 mg nicotine, and 7.0 mg CO), Philip Morris One (PM1; 1 mg tar, 0.1 mg nicotine, and 2.0 mg CO), EHCS EHCSSK6 (5 mg tar, 0.3 mg nicotine, and 0.6 mg CO), and EHCSS-K3 (3 mg tar, 0.2 mg nicotine, and 0.6 mg CO).
Tricker *et al.* [413] 2012b	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke** (Lark1 cigarettes containing 1.0 mg tar, 0.1 mg nicotine, and 1.5 mg carbon monoxide (CO)), and levels of urinary excretion of mutagenic material. The study involved the following three groups: smokers of Lark1 cigarettes; users of EHCSS-K3 cigarettes (3 mg tar, 0.2 mg nicotine, and 0.6 mg carbon monoxide (CO)); and non-smokers. Age: 20 to 50 years. Sex: 75 males 24 females Country: South Korea Data source: Korea Population size: Seventy-two subjects (54 males and 18 females) were randomized into 1 of 3 parallel groups (Lark1: N = 28; EHCSS-K3: N = 28; and no-smoking: N = 16) using a stratification based on median daily cigarette consumption (10–19 and 20–30 cigarettes per day) Trial duration: Enrolled subjects completed a 7-day smoking diary prior to check-in on Day -2 On Day -2, subjects entered the clinic before 08:00. All subjects were confined to the clinic from Day -2 to Day 9 under medical supervision. On Day -1 (baseline), assessments included determination of biomarkers of exposure in a 24-h urine sample, vital signs, COHb (COHb0700 and COHb17:00), plasma cotinine and nicotine (COT-P17:00 and NICP). E-cigarette, smoking and other related status: Adult male and female Korean smokers with acceptable health conditions who smoked 10–30 conventional combustible tobacco non-menthol cigarettes (1.0–3.0 mg tar) per day and the Lark1 (1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO) as their exclusive brand for at least 2 weeks prior to admission to the clinic were recruited. Outcomes: biomarkers of exposure to 10 of 12 selected conventional combustible tobacco cigarette smoke harmful and potentially harmful constituents • 1,3-Butadiene Monohydroxybutenyl mercapturic acid (MHBMA) • 2-Naphthylamine 2-Naphthylamine (2-NA) • 4-Aminobiphenyl 4-Aminobiphenyl (4-ABP) • Acrolein 3-Hydroxypropyl mercapturic acid (3-HPMA)

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		• Acrylamide Acrylamide mercapturic acid (AAMA) • Glycidamide mercapturic acid (GAMA) • Benzene S-Phenyl mercapturic acid (S-PMA) • CO Carboxyhemoglobin (COHb) • Crotonaldehyde 3-Hydroxy-1-methylpropyl mercapturic acid (3-HMPMA) • Nicotine Cotinine (COT-P) • Nicotine (NIC-P) • Nicotine equivalents (NEq)c • NNK Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) • Pyrene Total 1-hydroxypyrene (1-OHP)e • o-Toluidine o-Toluidine (o-TOL) • Mutagens Salmonella mutagenicity (YG1024 with S9) The authors concluded that the study showed **mean reductions in biomarkers of exposure to 10 of 12 selected harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke (1,3-butadiene, 2-naphthylamine, 4-aminobiphenyl, acrylamide, benzene, carbon monoxide (CO), nicotine, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), pyrene, and o-toluidine) from baseline to day 8 in Lark1 smokers who switched to smoking EHCSS-K3 cigarettes. No change was determined for biomarkers of exposure to crotonaldehyde and acrolein. In smokers who continued to smoke Lark1 cigarettes, exposure to the majority of the harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke (1,3-butadiene, 2-naphthylamine, 4-aminobiphenyl, acrylamide, benzene, carbon monoxide (CO), crotonaldehyde, nicotine, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and o-toluidine) increased, while biomarkers of exposure to acrolein and pyrene decreased. With the exception of 1,3-butadiene, 2-naphthylamine, benzene, carbon monoxide (CO), nicotine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), few of the changes reached the level of statistical significance.** The largest mean reductions in all harmful and potentially harmful constituents of conventional combustible tobacco cigarette smoke occurred in smokers who switched to no smoking. Excretion of mutagenic material in urine was significantly decreased in the EHCSS-K3 and no-smoking groups, and was significantly increased in the Lark1 group.[413] Device and products: A leading commercial conventional combustible tobacco cigarette brand (Lark One) was chosen to represent the Korean cigarette market in which smokers have a preference for smoking cigarettes with very low International Organization for Standardization (ISO) tar and nicotine yields. Lark1 also has a similar tobacco blend to that used in the EHCSS test cigarettes. Lark1 was analysed for tar and nicotine according to ISO methods. All study cigarettes were conditioned according to ISO standard 3402. Lark1 was smoked on a smoking machine according to ISO standard 3308 (International Organization for Standardization, 2000a). Tar, nicotine and CO were determined according to ISO standards 4387, 10315, and 8454, respectively (International Organization for Standardization, 2000b,c, 1995). Mainstream smoke from EHCSS cigarettes was generated on a modified smoking machine with a carousel adapted to use the EHCSS series-K lighter. The EHCSS smoke generation conformed with ISO standard 3308; some slight technical deviations were required. The ISO yields as declared on the cigarette packaging were as follows: Lark One (Lark1; 1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO) and EHCSS-K3 (3 mg tar, 0.2 mg nicotine, and 0.6 mg CO).
Tricker *et al.* [414] 2012c	Harm, but Less harmful than	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially harmful constituents of tobacco smoke** (in Marlboro cigarettes containing 6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide (CO)), and on levels of urinary excretion of mutagenic material. The study involved the following four groups: users of the

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
	conventional combustible tobacco cigarettes	EHCSS-K6 (5 mg tar, 0.3 mg nicotine, and 0.6 mg carbon monoxide (CO)); users of the EHCSS-K3 (3 mg tar, 0.2 mg nicotine, and 0.6 mg carbon monoxide (CO)); smokers who switched to smoking Lark1 cigarettes (1 mg tar, 0.1 mg nicotine, and 2.0 mg carbon monoxide (CO)); and non-smokers. Age: 19–50 years of age. Sex: 91 males and 40 females. Country: Japanese smokers Data source: Not reported Trial duration: All recruited subjects (N = 131; 91 males and 40 females) completed a 7-day diary prior to admission to the clinic during the morning on Day 2. All subjects were confined to the clinic from Day -2 to Day 9 under medical supervision. On Day 2, the eligibility for study inclusion was re-confirmed. Assessments included carbon monoxide carboxyhemoglobin, vital signs, and a physical examination. On Day -1, vital signs and a 12-lead ECG were measured, and blood samples drawn for clinical laboratory tests. On Day 0 (baseline), assessments included determination of biomarkers of exposure in a 24-h urine, vital signs, carbon monoxide carboxyhemoglobin, plasma cotinine and nicotine. On Day -2 through Day 0, subjects were only permitted to smoke M6J cigarettes. On Day 1 through Day 8 subjects smoked their randomized study cigarette or stopped smoking if they were randomized to the no-smoking group. Population size: All recruited subjects (N = 131; 91 males and 40 females). One hundred and twenty-eight subjects (89 males and 39 females) were randomized into 1 of 5 parallel groups (EHCSS-K3, EHCSS-K6, M6J, Lark1, and no-smoking; N = 28 per smoking group, and N = 16 in the no-smoking group) E-cigarette, smoking and other related status: Smokers with acceptable health conditions who had smoked 10–30 cigarettes per day were recruited. Subjects were to have smoked the Marlboro non-menthol cigarette (6 mg tar, 0.5 mg nicotine, and 7.0 mg carbon monoxide) as their exclusive brand for at least 2 weeks prior to study confinement. Outcomes: biomarkers of exposure to selected tobacco smoke harmful and potentially harmful constituents and excretion of mutagenic material in urine • 1,3-Butadiene Monohydroxybutenyl mercapturic acid (MHBMA) • 2-Naphthylamine 2-Naphthylamine (2-NA) • 4-Aminobiphenyl 4-Aminobiphenyl (4-ABP) • Acrolein 3-Hydroxypropyl mercapturic acid (3-HPMA) • Acrylamide Acrylamide mercapturic acid (AAMA) • Glycidamide mercapturic acid (GAMA) • Benzene S-Phenyl mercapturic acid (S-PMA) • Carbon monoxide Carboxyhemoglobin (COHb) • Crotonaldehyde 3-Hydroxy-1-methylpropyl mercapturic acid (3-HMPMA) • Nicotine Cotinine (COT-P) • Nicotine (NIC-P) • Nicotine equivalents (NEq)c • NNKb Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) • Pyrene Total 1-hydroxypyrene (1-OHP)e • o-Toluidine o-Toluidine (o-TOL) • Mutagens Salmonella mutagenicity (YG1024 with S9) The authors **concluded that this study showed statistically significant mean reductions in biomarkers of exposure to selected harmful and potentially harmful constituents in tobacco cigarette smoke and in excretion of mutagenic material in urine of smokers who smoke the M6J cigarette and switched to using the EHCSS K lighter and smoking either**

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		the EHCSS-K3 or the EHCSS-K6 cigarette at day 8, compared to baseline. In smokers who switched to smoking the Lark1 cigarette, a conventional combustible tobacco cigarette representative of the low-tar cigarette market, smaller mean reductions were observed, most of which were statistically significant. The largest mean reductions occurred in smokers who switched to no smoking.[414] Device and products: Conventional combustible tobacco cigarette brands were selected to include a leading market share cigarette on the Japanese market of similar ISO tar and nicotine yields to the EHCSS-K6 and a representative conventional combustible tobacco cigarette with a low ISO tar and nicotine yield. Both cigarettes also had a similar tobacco blend to that used in the EHCSS test cigarettes. Study cigarettes were analysed for tar and nicotine according to ISO methods. All study cigarettes were conditioned according to ISO standard 3402. Conventional combustible tobacco cigarettes were smoked on a smoking machine according to ISO standard 3308 (International Organization for Standardization, 2000a). Tar, nicotine and carbon monoxide were determined according to ISO standards 4387, 10315, and 8454, respectively.
Tricker *et al.* [415] 2012d	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure to 12 selected harmful and potentially harmful constituents in conventional combustible tobacco cigarette smoke** (Marlboro Ultra Lights Menthol cigarettes, the M4J(M) (4 mg tar and 0.3 mg nicotine)), and on levels of urinary excretion of mutagenic material and serum Clara cell 16-kDa protein (CC16) in the following four groups: smokers of conventional combustible tobacco cigarettes; users of the M4J(M) cigarettes; participants who switched to smoking either the EHCSS-K6M cigarette (5 mg tar and 0.3 mg nicotine) or the Lark1 menthol cigarette (Lark1M) (1 mg tar and 0.1 mg nicotine); and non-smokers. Age: 21–50 years of age. Sex: 62 males and 40 females Country: Japan Data source: Not reported Trial duration: The recruited subjects completed a 7-day diary prior to in-clinic admission on Day -3. On Day -3, the eligibility for study inclusion was re-confirmed. The subjects were confined to the clinic from Day 3 to Day 7 under medical supervision. Assessments included carbon monoxide carboxyhemoglobin and vital signs, and a physical examination. On Day 2, vital signs and a 12-lead ECG were measured, and blood samples drawn for clinical laboratory tests. On Day -1 and Day 0 (baseline days), assessments included determination of biomarkers of exposure in a 24-h urine sample, vital signs, serum, and plasma cotinine. On Day 0, one hundred subjects (61 males and 39 females) were randomized into 1 of 4 parallel groups (EHCSS-K6M, M4JM, Lark1M, and no-smoking; N = 28 per smoking group, and N = 16 in the no-smoking group). From Day 1 through Day 6, subjects participated in their assigned study groups. Population size: 102 E-cigarette, smoking and other related status: Adult male and female Japanese smokers with acceptable health conditions who smoked for at least a year, and had smoked exclusively 10–30 menthol cigarettes (3–6 mg tar yield) per day for at least 2 months were recruited Outcomes: biomarkers of exposure to selected conventional combustible tobacco cigarette smoke harmful and potentially harmful constituents • 1,3-Butadiene Monohydroxybutenyl mercapturic acid (MHBMA) • 2-Naphthylamine 2-Naphthylamine (2-NA) • 4-Aminobiphenyl 4-Aminobiphenyl (4-ABP) • Acrolein 3-Hydroxypropyl mercapturic acid (3-HPMA) • Acrylamide Acrylamide mercapturic acid (AAMA) • Glycidamide mercapturic acid (GAMA) • Benzene S-Phenyl mercapturic acid (S-PMA)

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		• Carbon monoxide Carboxyhemoglobin (COHb) • Crotonaldehyde 3-Hydroxy-1-methylpropyl mercapturic acid (3-HMPMA) • Nicotine Cotinine (COT-P) • Nicotine equivalents (NEq)c • NNKb Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) • Pyrene Total 1-hydroxypyrene (1-OHP)e • o-Toluidine o-Toluidine (o-TOL) • Mutagens Salmonella mutagenicity (YG1024 with S9) The authors concluded that this study showed **reductions in the mean values of individual biomarkers of exposure to selected harmful and potentially harmful constituents in tobacco cigarette smoke from baseline to day 5 or 6 in smokers of the M4J(M) cigarette who switched to using the EHCSS series-K lighter and smoking the EHCSS-K6M menthol cigarette. In smokers who switched to smoking the Lark1M menthol cigarette, a conventional combustible tobacco cigarette representative of the low-tar menthol cigarette market, reductions in exposure to individual harmful and potentially harmful constituents in tobacco cigarette smoke were smaller. The largest reductions in individual harmful and potentially harmful constituents in tobacco cigarette smoke occurred in smokers who switched to no smoking. Reductions in the mean excretion of mutagenic material in urine occurred in the EHCSS-K6M and no-smoking groups, but not in the M4J(M) and Lark1M groups. Changes in serum concentrations of Clara cell 16-kDa protein could not be meaningfully interpreted.**[415] Device and products: Conventional combustible tobacco cigarette brands were selected to include a leading market share cigarette of similar ISO tar and nicotine yields to the EHCSS-K6M and a representative conventional combustible tobacco cigarette with a low ISO tar and nicotine yield. The cigarettes also had a similar tobacco blend to that used in the EHCSS test cigarettes. Study cigarettes were analysed for tar and nicotine according to ISO methods. Study cigarettes were conditioned according to ISO standard 3402 (International Organization for Standardization, 1991). Conventional combustible tobacco cigarettes were smoked on a smoking machine according to ISO standard 3308. Tar and, nicotine were determined according to ISO standards 4387 and 10315, respectively (International Organization for Standardization, 2000b,c). These methods are essentially similar to methods used by the Tobacco Institute of Japan for declaration of tar and nicotine levels on cigarette packaging. Mainstream smoke from EHCSS cigarettes was generated on a modified smoking machine with a carousel adapted to use the EHCSS series-K lighter. The EHCSS smoke generation conformed with ISO standard 3308; some slight technical deviations were required. The ISO yields as declared on the cigarette packaging were as follows: Marlboro Ultra Lights Menthol (M4JM; 4 mg tar and 0.3 mg nicotine), Lark One Menthol (Lark1M; 1 mg tar and 0.1 mg nicotine), and EHCSS series-K menthol (EHCSS-K6M; 5 mg tar, 0.3 mg nicotine). All cigarettes used in the study contained menthol.
		Prototype heated cigarette
Sakaguchi *et al.* [416] 2014	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **changes in levels of biomarkers** of exposure in healthy smokers who switched to a prototype heated cigarette. Measures on 10 biomarkers of exposure (nicotine, carbon monoxide (CO), benzene, 1,3-butadiene, acrolein, hydrogen cyanide, crotonaldehyde, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), pyrene, and 4-aminobiphenyl), and urine mutagenicity, were recorded Age: 21–49 years. Sex: All males. Country: Japan Data source: Healthy Japanese male smokers Population size: 70 Trial duration: This study used a controlled, semi-randomized, open-label, parallel group, residential, 4-sites design. A total of 70 healthy Japanese male smokers were enrolled.

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		Following enrolment, subjects were admitted to the clinical study site for 2 days (baseline period) and stayed for four consecutive weeks (investigation period). On Day-1 and Day 0 (baseline period), the subjects were asked to smoke their usual brand of cigarettes in a manner like their routine smoking. On Day-1, participants could smoke at any time until bedtime (11:00 p.m.). On Day 0, subjects could smoke from the completion of medical check-up and blood and urine sampling in the morning to bedtime (11:00 p.m.). During the baseline period, the number of cigarettes smoked per day was approximately the same as their routine use. On Day 1 (first day of the investigation period), the subjects were allocated randomly either to the prototype heated cigarette group (47 smokers) or the conventional combustible tobacco cigarette 10 group (23 smokers) such that the ratio of sample size in the HC group and the conventional combustible tobacco cigarette 10 group was approximately 2:1. Assignment to study groups was stratified by age (21–30, 31–40 and 41–50 years) and BMI (<18.5, P18.5 to <25.0, P25.0) so that the prototype heated cigarette group and conventional combustible tobacco cigarette 10 group were evenly matched for these two parameters. Subjects were to smoke their assigned cigarettes in the smoking room. In the prototype heated cigarette and the conventional combustible tobacco cigarette 10 groups, each subject was to smoke in a prescribed controlled manner (i.e. smoking approximately 20 prototype heated cigarettes or conventional combustible tobacco cigarette 10s per day, eight puffs per cigarette) E-cigarette, smoking and other related status: Healthy Japanese male smokers aged who reported smoking at least 20 conventional combustible tobacco cigarettes (10–15 mg tar value, printed on the package) per day for more than one year and the same brand for at least eight weeks preceding screening were recruited. Outcomes: Nicotine equivalents and urine mutagenicity (specifically) • COHb - carboxyhemoglobin • Total NNAL - 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) plus NNAL-glucu-ronide • 4-ABP - 4-aminobiphenyl • 1-OHP - 1-hydroxypyrene • TMA - trans, trans-muconic acid • S-PMA - S-phenylmercapturic acid • MHBMA - monohydroxybutenylmercapturic acid • 3-HPMA - 3-hydroxypropylmercapturic acid • HMPMA - 3-hydroxyl-1-methylpropyl mercapturic acid • thiocyanate (SCN) a biomarker of exposure for hydrogen cyanide The authors **concluded that exposure to most tobacco cigarette smoke constituents, except carbon monoxide (CO), can be reduced by switching from a conventional combustible tobacco cigarette containing 10 mg tar to a prototype heated cigarette.**[416] Device and products: The reference cigarette, conventional combustible tobacco cigarette 10, was a commercially available cigarette brand in Japan with the values of 10 mg tar and 0.8 mg nicotine printed on the package. The test cigarette, prototype heated cigarette, was a prototype of a heat-not-burn tobacco product prepared by Japan Tobacco International.
		Tobacco heating system
Haziza *et al.* [417] 2016a	Harm, but Less harmful than conventiona l combustible	The authors reported on **levels of harmful and potentially harmful constituents** in smokers continuing to smoke conventional combustible tobacco cigarettes, smokers switching to the THS 2.2, and smokers abstaining from smoking for 5 days. Age: 23 to 65 years old. Sex: 80 males, 80 females. Country: Japanese smokers Data source: Study participants were recruited via the clinical site's database and through advertisements.

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
	tobacco cigarettes	Trial duration: This study was a controlled, randomized, 3-arm parallel, single centre study in confinement. The Screening Period covered a maximum of 4 weeks (Day -30 to Day -3) prior to admission and enrolment to the study site on Day -2. All subjects tested THS 2.2 using up to 3 THS Tobacco Sticks prior to enrolment. Eligible candidates were enrolled and confined under medical supervision until Discharge on Day 6. On Day -1 and Day 0 (Baseline), participants smoked their own preferred brand of conventional combustible tobacco cigarettes and baseline assessments were performed. On Day 0, 160 participants were randomized to THS 2.2 use (n = 80), conventional combustible tobacco cigarette smoking (n = 40) or to abstain from smoking (n = 40). From Day 1 to Day 5, participants in the THS 2.2 and conventional combustible tobacco cigarette groups used THS 2.2 or their own brand of non-menthol conventional combustible tobacco cigarettes, respectively, and exclusively. After Discharge on Day 6, or in case of an early discontinuation, participants entered a 7-day Safety Follow-Up Period for recording of spontaneously reported adverse events. During the designated smoking hours from 06:30 to 23:00, conventional combustible tobacco cigarette smoking was allowed ad libitum on Day -1 and Day 0, and depending on the participant's product allocation, exclusive use of THS 2.2 or exclusive. Twenty-four-hour urine was collected on each day. Conventional combustible tobacco cigarette smoking was allowed ad libitum from Day 1 to Day 5 Population size: 160. THS 2.2 use (n = 80), conventional combustible tobacco cigarette smoking (n = 40) or to abstain from smoking (n = 40) E-cigarette, smoking and other related status: Adult healthy Japanese smokers, were eligible if they smoked >=10 commercially available non-menthol conventional combustible tobacco cigarette s per day with a maximum yield of 1 mg nicotine per conventional combustible tobacco cigarette (ISO yield) for the last 4 weeks and had smoked conventional combustible tobacco cigarette for >= 3 consecutive years prior to enrolment. Outcomes: harmful and potentially harmful constituents: • Total NNAL [Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) • Total NNN [Total N-nitrosonornicotine] N-nitrosonornicotine (NNN) • MHBMA [Monohydroxybutenyl mercapturic acid] 1,3-butadiene • 3-HPMA [3-hydroxypropylmercapturic acid] Acrolein • S-PMA [S-phenylmercapturic acid] Benzene • COHb [Carboxyhemoglobin1] Carbon monoxide • Total 1-OHP [Total 1-hydroxypyrene] Pyrene • Total 3-OH-B[a]P [3-hydroxy-benzo(a)pyrene] Benzo(a)pyrene • 4-ABP [4-aminobiphenyl] 4-aminobiphenyl • 1-NA [1-aminonaphthalene] 1-aminonaphthalene • 2-NA [2-aminonaphthalene] 2-aminonaphthalene • o-tol [o-toluidine] o-toluidine • CEMA [2-cyanoethylmercapturic acid] Acrylonitrile • HEMA [2-hydroxyethylmercapturic acid] Ethylene oxide • 3-HMPMA [3-hydroxy-1-methylpropylmercapturic acid] Crotonaldehyde • S-BMA [S-benzylmercapturic acid] Toluene The **authors concluded that switching from smoking conventional combustible tobacco cigarettes to using the THS 2.2 resulted in substantial reductions in exposure to 15 selected harmful and potentially harmful constituents of tobacco smoke. The kinetics and the magnitude of the decrease in levels of biomarkers of exposure observed in the THS 2.2 group were approaching the levels observed in the smoking abstention group for**

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		the majority of the biomarkers of exposure. Nicotine uptake was similar between the THS 2.2 and conventional combustible tobacco cigarette groups at the end of the 5-day exposure period; after users had started to adapt to a new product, and with a transitional period of changing puffing behaviour, users were able to achieve their desired nicotine level. The combination of the results of nicotine exposure and subjective effect measures indicated that the THS 2.2 offered comparable satisfaction, with regard to taste and sensorial experience, to that which was observed in conventional combustible tobacco cigarette smokers. No adverse event or severe adverse events were reported during this study, with the total number of adverse events being very low and evenly balanced across study groups.[417] Device and products: The test product THS 2.2 was developed and provided by Philip Morris Products S.A. (part of Philip Morris International group of companies). THS 2.2 has three components: the THS tobacco Stick, the holder, and the charger. The THS tobacco stick contains a tobacco plug of processed tobacco cast leaf, which is covered by a paper wrap. The overall appearance of the THS tobacco stick is like that of a conventional combustible tobacco cigarette, except it is much shorter. The holder includes a battery, controlling electronics, and the heater element. The THS tobacco stick is inserted into the holder, and an electronically controlled heating blade within the holder heats the tobacco according to a carefully controlled temperature profile <350'C. The charger recharges the holder. To use THS 2.2, the THS tobacco stick is inserted into the holder, the heating of the THS tobacco stick is initiated by pressing the button on the holder and a LED indicates when the initial heating process is complete. The holder and THS tobacco stick are designed to deliver over approximately 6 min or around 14 puffs. At the end of each product use session, the THS holder requires recharging and for the next use a new THS tobacco stick must be used. The test product THS 2.2 contained 0.5 mg nicotine and 4.9 ± 0.5 mg/stick of glycerine as determined under ISO conditions using machine puffing methods. The reference product in this study were the participants' own preferred brand of non-menthol conventional combustible tobacco cigarettes used in the conventional combustible tobacco cigarette group. Conventional combustible tobacco cigarettes were not provided by the sponsor, and subjects were asked to buy and bring their own conventional combustible tobacco cigarette s to the investigational site.
Haziza *et al.*[418] 2016b	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on levels of **harmful and potentially harmful constituents** in smokers continuing to smoke conventional combustible tobacco cigarettes, smokers switching to the THS 2.2, and smokers abstaining from smoking for 5 days. Age: 21 to 65 years Sex: 80 males, 80 females. Country: Adult Caucasian in Poland Data source: Study participants were recruited via the clinical site's database and through advertisements Trial duration: This study was designed as a controlled, randomized, three arm parallel, single-centre study in confinement. The Screening Period covered a maximum of 4 weeks (Day -30 to Day -3) prior to Admission on Day -2 to the study site. Prior to enrolment on Day -2, as the last procedure of the eligibility assessments on that day, all subjects participated in a product trial of THS 2.2 (using up to three THS 2.2 tobacco sticks. On Day -2, after all inclusion/exclusion criteria had been met, eligible candidates were enrolled and confined under medical supervision until Discharge on Day 6. On Day -1 and Day 0, participants smoked their own preferred brand of conventional combustible tobacco cigarette s for baseline assessments. From Day 1 to Day 5, participants in the THS and conventional combustible tobacco cigarette groups used, respectively, THS 2.2 or their own brand of non-menthol conventional combustible tobacco cigarettes exclusively. Participants in the smoking abstinence arm were asked to completely abstain from smoking from Day 1 to Day 5. No participant could use any supportive medication for smoking abstention. On Day 6 or on the day of early discontinuation, end of study procedures was conducted. After discharge on Day 6, or in case of an early discontinuation, participants entered a 7-day Safety Follow-Up Period for recording of spontaneously reported new adverse events, serious adverse events, or follow-up of any ongoing adverse event/serious adverse event that occurred during confinement. From Day 1 to Day 5, for

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		conventional combustible tobacco cigarette, and from Day 1 to Day 5 for THS 2.2, product use was allowed during the designated product use hours from 06:30 to 23:00 ad libitum, and 24-h urine was collected on each day. Population size: 160. THS 2.2 use (n = 80), conventional combustible tobacco cigarette smoking (n = 40) or to abstain from smoking (n = 40) Data collection period: The study was conducted between June and September 2013 at BioVirtus Research Site (Kajetany, Poland) E-cigarette, smoking and other related status: Adult Caucasian smokers aged 21e65 years were eligible for participation in the study. Potential participants were eligible if they smoked >=10 commercially available non-menthol conventional combustible tobacco cigarettes per day with a maximum yield of 1 mg nicotine per cigarette (ISO yield) for the last 4 weeks and had smoked CC for >=3 consecutive years before enrolment Data source: Study participants were recruited via the clinical site's database and through advertisements Outcomes: reported by acronym [biomarker of exposure] (harmful or potentially harmful smoke constituent) o Total NNAL [Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] 4-(methylnitros-amino)-1-(3-pyridyl)-1-butanone (NNK) o Total NNN [Total N-nitrosonornicotine] N-nitrosonornicotine (NNN) o MHBMA [Monohydroxybutenyl mercapturic acid] 1,3-butadiene o 3-HPMA [3-hydroxypropylmercapturic acid] Acrolein o S-PMA [S-phenylmercapturic acid] Benzene o COHb [Carboxyhemoglobin1] Carbon monoxide o Total 1-OHP [Total 1-hydroxypyrene] Pyrene o Total 3-OH-B[a]P [3-hydroxy-benzo(a)pyrene] Benzo(a)pyrene o 4-ABP [4-aminobiphenyl] 4-aminobiphenyl o 1-NA [1-aminonaphthalene] 1-aminonaphthalene o 2-NA [2-aminonaphthalene] 2-aminonaphthalene o o-tol [o-toluidine] o-toluidine o CEMA [2-cyanoethylmercapturic acid] Acrylonitrile o HEMA [2-hydroxyethylmercapturic acid] Ethylene oxide o 3-HMPMA [3-hydroxy-1-methylpropylmercapturic acid] Crotonaldehyde o S-BMA [S-benzylmercapturic acid] Toluene The authors **concluded that biomarkers of exposure, except those associated with nicotine exposure, were significantly reduced in the THS 2.2 group compared with the conventional combustible tobacco cigarette group, and approached the levels observed in the smoking abstinence group. Increased product consumption and total puff volume were reported in the THS 2.2 group. However, exposure to nicotine was similar to that in the conventional combustible tobacco cigarette group at the end of the confinement period. Reduction in the urge to smoke was comparable between the THS 2.2 and conventional combustible tobacco cigarette groups, and the THS 2.2 product was well tolerated**.[418] Device and products: The THS 2.2 product was developed and provided by Philip Morris Products S.A. (part of Philip Morris International group of companies). The product is described in part 1 of this series (Smith *et al.*., 2016). Briefly, THS 2.2 has three components: the tobacco stick, the holder, and the charger. The tobacco stick (FR1 blend) contains a tobacco plug of processed tobacco cast leaf, which is enclosed in a paper wrap. The overall appearance of the tobacco stick is like a conventional combustible tobacco cigarette, except it is much shorter. The holder includes a battery, controlling electronics, and the heating element. The tobacco stick is inserted into the holder, and an electronically controlled heating blade heats the tobacco according to a carefully controlled temperature profile to temperatures not exceeding 300 C. The charger recharges the holder. To use THS 2.2, the tobacco stick is inserted into the holder and the

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		heating of the tobacco stick is initiated by pressing the button on the holder. An LED indicates when the initial heating process is complete. The holder and tobacco stick are designed for a usage period of approximately 6 minutes or for around 14 puffs. The holder must be recharged after each usage period of 6 min and a new tobacco stick must be used for the next usage cycle. The THS 2.2 test product contained 0.5 mg nicotine as determined under ISO conditions and 56.4 mg/stick of glycerine as aerosol former. The reference product in this clinical study were the participant's own preferred brand of non-menthol conventional combustible tobacco cigarettes used in the conventional combustible tobacco cigarette group. Conventional combustible tobacco cigarettes were not provided by the Sponsor, and subjects were asked to buy and bring their own conventional combustible tobacco cigarettes to the investigational site.
Haziza *et al.*[419] 2020	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on **levels of biomarkers of exposure** in smokers continuing to smoke conventional combustible tobacco cigarettes, smokers switching to the menthol THS 2.2, and smokers abstaining from smoking for 5 days in a confined setting, followed by an 86-day ambulatory period. Age: 37.7 ± 11.45. Sex: 96 males, 64 females. Country: White (99), Black or African American (51), Other (9), Missing (1) Data source: The study was conducted in Dallas, Texas, and Daytona Beach, Florida Trial duration: The study was composed of four main periods. After the screening period, from day −30 to day −3, which included a product trial, subjects were enrolled (day −2) and randomized (day 0) in a 2:1:1 ratio to the mTHS, menthol Conventional combustible tobacco cigarettes, and smoking abstinence groups. The 5-day confinement period (day 1 to day 5) was followed by an 86-day ambulatory period (day 6 to day 91) and an additional 28-day safety follow-up period in order to record spontaneously reported new adverse events or serious adverse events and to monitor the active follow-up of ongoing adverse events and serious adverse events by the site. On day −1 and day 0, all subjects smoked their own brand of menthol conventional combustible tobacco cigarettes for baseline assessments. During the confinement period, subjects in the mTHS and menthol conventional combustible tobacco cigarettes groups used exclusively ad libitum mTHS or their own brand of menthol conventional combustible tobacco cigarettes, respectively, during the designated smoking hours (06:30 am–11:00 pm). Subjects in the smoking abstinence group were asked to abstain from tobacco product use completely. On day 6, subjects were discharged from the study site and instructed to continue using their assigned product or to abstain from smoking for 86 days. Subjects were required to make three monthly visits of two consecutive days including one overnight stay each (day 30, 60, and 90) at the investigational site. Population size: The safety population included 165 subjects who had tried mTHS, of which 160 (full analysis set) were randomized to mTHS (80), menthol conventional combustible tobacco cigarettes (41), and smoking abstinence (39). Data collection period: December 2013 and October 2014 E-cigarette, smoking and other related status: Healthy male and female US smokers were eligible. Outcomes: Biomarkers of exposure: • Total NNAL [Total NNAL was determined as the molar sum of 4-(methylnitrosamino)-1-(3-pyridy1)-1-butanol and its O-glucuronide conjugate] • Total NNN [Total NNN was determined as the molar sum of free and conjugated NNN i.e.N-nitrosonornicotine] • COHb (%) [carboxyhemoglobin] • MHBMA [monohydroxybutenyl mercapturic acid]

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		• 3-HPMA [3-hydroxypropylmercapturic acid] • S-PMA [S-phenylmercapturic acid] • Total 1-OHP [1-hydroxypyrene] • 4-ABP [4-aminobiphenyl] • 1-NA [1-aminonaphthalene] • 2-NA [2-aminonaphthalene] • o-tol [o-toluidine] • CEMA [Cyanoethylmercapturic Acid] • HEMA [Hydroxybutyl Mercapturic Acid] • HMPMA [Not named in full] • B[a]P [benzo[a]pyren] • NEQ [nicotine equivalent] The authors concluded **that switching to the menthol THS 2.2 led to significant reductions in exposure to Total NNAL the molar sum of 4-(methylnitrosamino)-1-(3-pyridy1)-1-butanol and its O-glucuronide conjugate, Total NNN the molar sum of free and conjugated NNN i.e.N-nitrosonornicotine, carboxyhemoglobin, monohydroxybutenyl mercapturic acid, 3-hydroxypropylmercapturic acid, S-phenylmercapturic acid1-hydroxypyrene, 4-aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, o-toluidine, Cyanoethylmercapturic Acid, Hydroxybutyl Mercapturic Acid, HMPMA, and benzo[a]pyren after 5 days in confinement, which were maintained throughout the subsequent ambulatory period of 86 days. The reductions were comparable to those observed upon smoking abstinence**.[419] Device and products: The investigational product was mTHS 2.2. Maximum heating temperature is 350°C; per stick, menthol (2.62 mg/stick), nicotine (1.21 mg/stick), and glycerine (3.94 mg/stick) yields were obtained under the Health Canada Intense smoking regimen. Reference products were menthol conventional combustible tobacco cigarettes of the subjects' preferred commercially available brands. Cigarettes were not provided to the subjects, who were asked to purchase their own preferred brand. Heatsticks, together with the THS 2.2 device, were provided to the subjects as THS 2.2 was not commercialized in the United States.
Lüdicke *et al.* [421] 2017	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors reported on the impact of switching to the THS 2.1 on biomarkers of **exposure to harmful and potentially harmful constituents.** Age mean (SD): 23 to 65 years Sex: Country: Not reported Data source: Subjects were recruited via the clinical site's database and through advertisements. Trial duration: Five days Population size:42 E-cigarette, smoking and other related status: current smokers Outcomes: harmful or potential harmful smoking constituents • COHb - carboxyhaemoglobin • 3-HPMA - 3-hydroxypropylmercapturic acid

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		• MHBMA - monohydroxybutenyl mercapturic acid • S-PMA - S-phenylmercapturic acid • Total NNAL -4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; • 1-OHP - 1-hydroxypyrene • Total NNN - determined as the molar sum of 4-(methylnitrosamino)-1-(3-pyridy1)-1-butanol and its O-glucuronide conjugate • 4-ABP - 4-aminobiphenyl; • 2-NA - 2-aminonaphthalene • o-tol -o-toluidine • CEMA - 2-cyanoethylmercapturic acid • NEQ – nicotine equivalent • Nicotine • Cotinine The authors concluded that **the THS 2.1 is a promising alternative to smoking conventional combustible tobacco cigarettes. Notwithstanding possible use adaption through consumption or puffing behaviour, the exposure to harmful smoke constituents was markedly reduced following use of the new heat-not-burn tobacco product platform.**[421] Device and products: The test product THS 2.1 contain 0.3 mg nicotine and 50 mg glycerol as aerosol former determined under smoke chemistry ISO conditions (12 puffs). It was developed by Philip Morris International and provided by the Sponsor. THS 2.1 has three components: the THS tobacco stick, the holder, and the charger. The THS tobacco stick has a tobacco plug containing processed tobacco cast leaf, which is covered by a paper wrap. The holder includes a battery, controlling electronics, and the heater element. The THS tobacco stick is inserted into the holder and heats the tobacco via an electronically controlled heating blade. The charger recharges the holder. The THS tobacco sticks were preheated for 30 seconds in the THS holder and the energy capacity of the holder was sufficient to maintain a product use session for up to 6 minutes. At the end of each product use session, the THS holder required recharging. The reference product in this study was nonmenthol conventional combustible tobacco cigarettes of the subject's own preferred commercially available brand. Conventional combustible tobacco cigarettes were not provided by the Sponsor, and subjects were asked to buy and bring their own conventional combustible tobacco cigarette s to the investigational site.
Lüdicke *et al.* [422] 2018b	Harm, but Less harmful than conventiona l combustible tobacco cigarettes	The authors reported on the impact of switching to the menthol THS 2.2 on **biomarkers of exposure to harmful and potentially harmful constituents** relative to smoking menthol conventional combustible tobacco cigarettes and smoking abstinence. Age mean (SD): 37.2 +/- 10.54 years. Sex: 68 males 92 females. Country: Japan. Ethnicity: Japanese adult smokers Data source: Japanese smokers were recruited via the clinical site's database and via advertisements. Trial duration: The study comprised a 4-week screening period (days −30 to −3), a confinement period (days −2 to 6), an 85-day ambulatory period (days 6–91) and a 28-day safety follow-up period for the recording of spontaneously reported adverse events or serious adverse events. On days −1 and 0, participants smoked their own brand of menthol conventional combustible tobacco cigarettes and underwent baseline assessments. On day 1, the participants were randomized to one of three groups in a 2:1:1 ratio to switch to Menthol Tobacco Heating System (Menthol Tobacco Heating System group), continue smoking menthol conventional combustible tobacco cigarettes, or abstain from smoking (smoking abstinence group), respectively. Randomization was performed with stratification by sex and daily average menthol conventional combustible tobacco cigarette

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		consumption (10–19 vs. >19 menthol conventional combustible tobacco cigarettes/day). Between days 1 and 5, participants in the Menthol Tobacco Heating System and menthol conventional combustible tobacco cigarettes groups used the allocated product ad libitum during the designated smoking hours (06:30 am to 11:00 pm), while participants in the smoking abstinence group completely abstained from smoking. During the 85-day ambulatory period, the participants returned to the study site and stayed overnight on the days 30, 60, and 90 visits. Population size: The full analysis set comprised 160 participants, randomized as follows: 78 to switching to menthol Tobacco Heating System, 42 to continuing smoking menthol conventional combustible tobacco cigarettes, and 40 to smoking abstinence, of which two, one, and two participants, respectively, voluntarily discontinued. The safety analysis (n = 175) contained the 15 subjects who tried the menthol Tobacco Heating System but were discontinued from enrolment, and thus, not randomized. E-cigarette, smoking and other related status: Persons who smoked ≥10 commercially available menthol conventional combustible tobacco cigarettes per day (self-reported) in the last 4 weeks (maximum yield of 1 mg nicotine per cigarette), and if they reported to have smoked menthol conventional combustible tobacco cigarettes for ≥3 years Outcomes: • Total NNAL -4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; • Total NNN - determined as the molar sum of 4-(methylnitrosamino)-1-(3-pyridy1)-1-butanol and its O-glucuronide conjugate • COHb - carboxyhemoglobin; • MHBMA - monohydroxybutenyl mercapturic acid • 3-HPMA - 3-hydroxypropylmercapturic acid • S-PMA - S-phenylmercapturic acid • Total 1-OHP - determined as the molar sum of 1-hydroxypyrene and its glucuronide and sulfate conjugates • 4-ABP - 4-aminobiphenyl; • 1-NA - 1-aminonaphtalene • 2-NA - 2-aminonaphthalene • o-tol -o-toluidine • CEMA - 2-cyanoethylmercapturic acid • HEMA - 2-hydroxyethylmercapturic acid • 3-HMPMA - 3-hydroxy-1-methylpropylmercapturic acid • 3-OH-B[a]P -3-hydroxy(a)benzopyrene • NEQ – nicotine equivalent The authors **concluded that switching from menthol conventional combustible tobacco cigarettes to the menthol THS 2.2 significantly reduced exposure to harmful and potentially harmful constituents relative to continuing smoking menthol conventional combustible tobacco cigarettes, with concentrations in those who switched being similar to the concentrations observed following smoking abstinence in Japanese adult smokers**.[422] Device and products: The menthol Tobacco Heating System (2.62 mg/stick of menthol, 1.21 mg/stick of nicotine, and 3.94 mg/stick of glycerine used as aerosol former, obtained under Health Canada Intense smoking regimen, maximum heating temperature 350°C) was used in this study. Reference products were menthol conventional combustible tobacco cigarettes of the participant's preferred commercially available brand.
		Carbon-heated tobacco product

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
Lüdicke *et al.* [420] 2016	Harm, but Less harmful than conventional combustible tobacco cigarettes	The authors aimed to investigate the effects of exposure to selected **harmful and potentially harmful constituents** of conventional combustible tobacco cigarette smoke in adult smokers who switched to a carbon-heated tobacco product, compared with adult smokers who continued to smoke conventional combustible tobacco cigarettes and those who abstained from smoking for 5 days. Age mean (SD) years: carbon-heated tobacco product group 36 (8.2); combustible tobacco cigarettes group 35.4 (7.4); abstinence group 37.9 (8.4) sex: 56 males, 56 females; country: single-centre confinement study conducted in Warsaw, Poland. Data source: Not reported Trial duration: Controlled, randomized, open-label, three-arm parallel group. Eligible subjects were enrolled on Day −2. (Admission) Subjects were randomly assigned into one of the three study arms by an interactive voice response system. The study was conducted in four successive cohorts. All subjects of a cohort were randomly assigned in the evening of Day 0 (D0). Randomization was stratified by sex and self-reported daily conventional combustible tobacco cigarette consumption (10−19 conventional combustible tobacco cigarettes per day [cpd] and 20−30 cpd). During the 2-day baseline period (D −1 and D0), subjects smoked their own brand of conventional combustible tobacco cigarettes ad libitum with each subject's maximum daily conventional combustible tobacco cigarette consumption limited to 120% of the median daily conventional combustible tobacco cigarette consumption, derived from a 7-day self-reported conventional combustible tobacco cigarette consumption diary recorded prior to admission. The exposure period lasted 5 days (D1−D5). During the exposure period, conventional combustible tobacco cigarette smoking or carbon-heated tobacco product use was allowed ad libitum in separate rooms until 11:00 PM. Subjects using the carbon-heated tobacco product did not have access to conventional combustible tobacco cigarettes and vice versa. Participants in the smoking abstinence group were denied access to these rooms and underwent counselling on smoking cessation, but no pharmacotherapy. Subjects were discharged during the morning of D6 after undergoing all safety examination procedures. They entered a 7-day passive adverse event follow-up period Population size: 112 subjects were randomly assigned into one of the three study groups (carbon-heated tobacco product: 56 subjects, conventional combustible tobacco cigarette: 28 subjects, smoking abstinence: 28 subjects; full analysis set). Data collection period: Not reported E-cigarette, smoking and other related status: Smoking habit of 10−30 cigarettes per day (maximum International Organization for Standardization [ISO] tar yield of 10 mg), smoking history of at least 5 consecutive years Outcomes: Biomarkers of exposure assessed as part of this study were • COHb (biomarker for carbon monoxide), • MHBMA (biomarker for 1,3-butadiene), 3-HPMA (biomarker for acrolein), • total 1-OHP (biomarker for pyrene), • O-toluidine (biomarker for ortho-toluidine), • 2-NA (biomarker for 2-aminonaphthalene), • 4-ABP (biomarker for 4-aminobiphenyl), • S-PMA (biomarker for benzene), • total NNAL (biomarker for NNK) and • nicotine equivalents (biomarker of exposure for nicotine) and

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		• cotinine (biomarker of exposure for nicotine) Switching to the carbon-heated tobacco product or smoking abstinence resulted in marked decreases from baseline to Day 5 in all biomarkers of exposure measured, including carboxyhaemoglobin (43% and 55% decrease in the carbon-heated tobacco product and SA groups, respectively). The urinary excretion of mutagenic material was also markedly decreased on Day 5 compared with baseline (89% and 87% decrease in the carbon-heated tobacco product and smoking abstinence groups, respectively). No changes in biomarkers of exposure to harmful and potentially harmful constituents or urinary mutagenic material were observed between baseline and Day 5 in the conventional combustible tobacco cigarette group. The authors **concluded that the results provide clear evidence supporting a reduction in the level of exposure to harmful and potentially harmful constituents of tobacco cigarette smoke in smokers who switched to a carbon-heated tobacco product under controlled conditions, and that the reduction was similar to that observed in the smoking abstinence group**.[420] Device and products: The carbon-heated tobacco product prototype MD2-E7 (3 mg tar, 2 mg glycerol, 0.4 mg nicotine, and 1 mg carbon monoxide yield; aerosol chemistry determined under ISO conditions, 12 puffs). It consists of a carbon heat source, a tobacco plug wrapped in paper, an empty tube (to allow aerosol transfer), and a filter (a strip of aluminium foil that attaches the carbon heat source to the tobacco plug). Its appearance is like that of a combustible cigarette, but the carbon-heated tobacco product is based on technology that avoids pyrolysis/ combustion of tobacco. The aerosol chemistry of the carbon-heated tobacco product was previously reported.9 The test product and a specifically designed electric lighter were provided to the subjects. Reference and baseline products were commercially available non-menthol combustible cigarettes, with an ISO tar yield of up to 10 mg. All subjects purchased the anticipated amount of their usual combustible cigarettes brand required for the confinement period and handed them over to the site staff at admission. All products were stored at room temperature in a locked room with restricted access. Used combustible cigarettes and carbon-heated tobacco product were returned to the site product accountability.
		glo™ THP 1.0 versus IQOS/THS
Gale *et al.*[423] 2018	Both heat-not-burn products equal	The authors reported on the relationship of using two tobacco heating products (the glo™ THP 1.0 or the in-market comparator, the IQOS/THS) with **biomarkers of toxicant exposure.** Age mean age range: 31 to 35 years. Sex: A male:female ratio of 1:1. Country: Japan Ethnicity: Japanese Data source: Healthy male and female smokers Population size: Overall 182 participants were enrolled into the study on day –1 and randomized to one of the six study groups. During the baseline period, two participants were withdrawn from the study. 180 participants entered the exposure period and completed the study in accordance with the protocol Trial duration: The study ranged from baseline to end of study (days 6–7). For biomarker data, the mean of the two values taken prior to first randomized product use (i.e. days –1 to 1 and days 1–2) was used as the baseline value. E-cigarette, smoking and other related status: All subjects had a smoking history of at least 3 years and smoked between 10 and 30 cigarettes daily Outcomes: Urinary biomarkers of toxicant exposure: total nicotine equivalents (TNeq; nicotine, cotinine, 3-hydroxycotinine, and their glucuronide conjugates); total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL); total N-nitrosonornicotine (NNN); 3-hydroxypropylmercapturic acid (3-HPMA); 3-hydroxy-1-methylpropylmercapturic acid (HMPMA); S-phenylmercapturic acid (S-PMA); monohydroxybutenyl-mercapturic acid

Author(s), year	Possible benefit or harm	Interventional trial papers on exposure to heat-not-burn toxins
		(MHBMA); 2-cyanoethylmercapturic acid (CEMA); 4-aminobiphenyl (4-ABP); o-toluidine (o-Tol); 2-aminonaphthalene (2-AN); 1-hydroxypyrene (1-OHP); 2-hydroxyethylmercapturic acid (HEMA); N-acetyl-S-(2-carbamoylethyl)cysteine (AAMA); and N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (GAMA) The authors **concluded that glo™ or IQOS use for 5 days reduced exposure to smoke toxicants in a manner comparable to quitting tobacco use. The tobacco heating system product reduced exposure to tobacco products with that glo™ or IQOS have the potential to be regarded as modified risk tobacco products.**[423] Device and products: A 7-mg/cig ISO tar combustible tobacco non-menthol cigarette, glo™/THP1.0 with non-menthol Neostiks, a 7-mg/cig ISO tar combustible tobacco menthol cigarette, and glo™/THP1.0 with menthol Neostiks.

Appendix 7: Interventional trials papers on e-cigarettes by industry authors

1. Cravo AS, Bush J, Sharma G, et al.[392] A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regul Toxicol Pharmacol* 2016;81 Suppl 1:S1-S14. doi: 10.1016/j.yrtph.2016.10.003
2. D'Ruiz CD, O'Connell G, Graff DW, et al. [364]Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regul Toxicol Pharmacol* 2017;87:36-53. doi: 10.1016/j.yrtph.2017.05.002
3. O'Connell G, Graff DW, D'Ruiz CD. [380]Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Toxicol Mech Methods* 2016;26(6):443-54. doi: 10.1080/15376516.2016.1196282
4. O'Connell G, Pritchard JD, Prue C, et al. [318]A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med* 2019;14(6):853-61. doi: 10.1007/s11739-019-02025-3
5. Stiles MF, Campbell LR, Graff DW, et al.[331] Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: implications for abuse liability. *Psychopharmacology (Berl)* 2017;234(17):2643-55. doi: 10.1007/s00213-017-4665-y
6. Walele T, Bush J, Koch A, et al.[393] Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-life setting. *Regul Toxicol Pharmacol* 2018;92:226-38. doi: 10.1016/j.yrtph.2017.12.010
7. Yan X, D'Ruiz C.[340] Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul Toxicol Pharmacol* 2015;71(1):24-34. doi: 10.1016/j.yrtph.2014.11.004
8. Yuki D, Sakaguchi C, Kikuchi A, et al.[386] Pharmacokinetics of nicotine following the controlled use of a prototype novel tobacco vapor product. *Regul Toxicol Pharmacol* 2017;87:30-35. doi: 10.1016/j.yrtph.2017.05.005

Appendix 8: List of harmful and potentially harmful constituents of tobacco smoke

The FDA has established a list of harmful and potentially harmful constituents, as required by the Federal Food, Drug, and Cosmetic Act.[452] The list consists of 93 named harmful and potentially harmful constituents. The harmful and potentially harmful constituents are reported to be: carcinogenic, toxic (to the respiratory, cardiovascular, and/or reproductive systems or development of the embryo or foetus), or addictive. Specifically, there are 79 named carcinogens, 25 respiratory toxins, 12 cardiovascular toxins, and 14 reproductive or developmental toxins. Some constituents adversely impact on health in more than one way.[452]

Harmful and potentially harmful constituents	Addictive substance	Cardiovascular toxicant	Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	Banned in food
Total	**4**	**12**	**79**	**25**	**14**	
Acetaldehyde	Addictive substance		Carcinogen	Respiratory toxicant		
Acetamide			Carcinogen			
Acetone				Respiratory toxicant		
Acrolein		Cardiovascular toxicant		Respiratory toxicant		
Acrylamide			Carcinogen			
Acrylonitrile			Carcinogen	Respiratory toxicant		
Aflatoxin B1			Carcinogen			
4-Aminobiphenyl			Carcinogen			
1-Aminonaphthalene			Carcinogen			
2-Aminonaphthalene			Carcinogen			
Ammonia				Respiratory toxicant		
Anabasine	Addictive substance					
o-Anisidine			Carcinogen			
Arsenic		Cardiovascular toxicant	Carcinogen		Reproductive or developmental toxicant	
A-α-C (2-Amino-9H-pyrido[2,3-b]indole)			Carcinogen			
Benz[a]anthracene		Cardiovascular toxicant	Carcinogen			
Benz[j]aceanthrylene			Carcinogen			
Benzene		Cardiovascular toxicant	Carcinogen		Reproductive or developmental toxicant	
Benzo[b]fluoranthene		Cardiovascular toxicant	Carcinogen			
Benzo[k]fluoranthene		Cardiovascular toxicant	Carcinogen			

Harmful and potentially harmful constituents	Addictive substance	Cardiovascular toxicant	Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	Banned in food
Benzo[b]furan			Carcinogen			
Benzo[a]pyrene			Carcinogen			
Benzo[c]phenanthrene			Carcinogen			
Beryllium			Carcinogen			
1,3-Butadiene			Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	
Cadmium			Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	
Caffeic acid			Carcinogen			
Carbon monoxide					Reproductive or developmental toxicant	
Catechol			Carcinogen			
Chlorinated dioxins/furans			Carcinogen		Reproductive or developmental toxicant	
Chromium			Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	
Chrysene		Cardiovascular toxicant	Carcinogen			
Cobalt		Cardiovascular toxicant	Carcinogen			
Coumarin						Banned in food
Cresols (o-, m-, and p-cresol)			Carcinogen	Respiratory toxicant		
Crotonaldehyde			Carcinogen			
Cyclopenta[c,d]pyrene			Carcinogen			
Dibenz[a,h]anthracene			Carcinogen			
Dibenzo[a,e]pyrene			Carcinogen			
Dibenzo[a,h]pyrene			Carcinogen			
Dibenzo[a,i]pyrene			Carcinogen			
Dibenzo[a,l]pyrene			Carcinogen			
2,6-Dimethylaniline			Carcinogen			
Ethyl carbamate (urethane)			Carcinogen		Reproductive or developmental toxicant	
Ethylbenzene			Carcinogen			

Harmful and potentially harmful constituents	Addictive substance	Cardiovascular toxicant	Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	Banned in food
Ethylene oxide			Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	
Formaldehyde			Carcinogen	Respiratory toxicant		
Furan			Carcinogen			
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole)			Carcinogen			
Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole)			Carcinogen			
Hydrazine			Carcinogen	Respiratory toxicant		
Hydrogen cyanide		Cardiovascular toxicant		Respiratory toxicant		
Indeno[1,2,3-cd]pyrene			Carcinogen			
IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)			Carcinogen			
Isoprene			Carcinogen			
Lead		Cardiovascular toxicant	Carcinogen		Reproductive or developmental toxicant	
MeA-α-C (2-Amino-3-methyl)-9H-pyrido[2,3-b]indole)			Carcinogen			
Mercury			Carcinogen		Reproductive or developmental toxicant	
Methyl ethyl ketone				Respiratory toxicant		
5-Methylchrysene			Carcinogen			
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)			Carcinogen			
Naphthalene			Carcinogen	Respiratory toxicant		
Nickel			Carcinogen	Respiratory toxicant		
Nicotine	Addictive substance				Reproductive or developmental toxicant	
Nitrobenzene			Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	
Nitromethane			Carcinogen			
2-Nitropropane			Carcinogen			

Harmful and potentially harmful constituents	Addictive substance	Cardiovascular toxicant	Carcinogen	Respiratory toxicant	Reproductive or developmental toxicant	Banned in food
N-Nitrosodiethanolamine (NDELA)			Carcinogen			
N-Nitrosodiethylamine			Carcinogen			
N-Nitrosodimethylamine (NDMA)			Carcinogen			
N-Nitrosomethylethylamine			Carcinogen			
N-Nitrosomorpholine (NMOR)			Carcinogen			
N-Nitrosonornicotine (NNN)			Carcinogen			
N-Nitrosopiperidine (NPIP)			Carcinogen			
N-Nitrosopyrrolidine (NPYR)			Carcinogen			
N-Nitrososarcosine (NSAR)			Carcinogen			
Nornicotine	Addictive substance					
Phenol		Cardiovascular toxicant		Respiratory toxicant		
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine)			Carcinogen			
Polonium-210			Carcinogen			
Propionaldehyde		Cardiovascular toxicant		Respiratory toxicant		
Propylene oxide			Carcinogen	Respiratory toxicant		
Quinoline			Carcinogen			
Selenium				Respiratory toxicant		
Styrene			Carcinogen			
o-Toluidine			Carcinogen			
Toluene				Respiratory toxicant	Reproductive or developmental toxicant	
Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole)			Carcinogen			
Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole)			Carcinogen			
Uranium-235			Carcinogen	Respiratory toxicant		
Uranium-238			Carcinogen	Respiratory toxicant		
Vinyl acetate			Carcinogen	Respiratory toxicant		
Vinyl chloride			Carcinogen			

HRB
Health
Research
Board