Jerisha Ellerstrand, Alize Ferrari, Louisa Degenhardt, Harvey Whiteford & Janni Leung

A systematic review of the global prevalence of prescription opioid non-medical use with an estimate of prescription opioid dependence

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A SYSTEMATIC REVIEW OF THE GLOBAL PREVALENCE OF PRESCRIPTION OPIOID NON-MEDICAL USE - WITH AN ESTIMATE OF PRESCRIPTION OPIOID DEPENDENCE

Jerisha Ellerstrand, Alize Ferrari,
Louisa Degenhardt, Harvey Whiteford & Janni Leung

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List of Abbreviations

BOD	Burden of disease
BZD	Benzodiazepine
CI	Confidence interval
DALY	Disability Adjusted Life Year
DSM	Diagnostic and Statistical Manual
DSM-IV	Diagnostic and Statistical Manual fourth edition
DSM-IV TR	Diagnostic and Statistical Manual fourth edition (text revision)
DSM-5	Diagnostic and Statistical Manual fifth edition
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
g	grams
GBD	Global Burden of Disease
HIS	High Income Super-region
ICD	International Classification of Diseases
IHME	Institute for Health Metrics and Evaluation
NDSHS	National Drug Strategy Household Survey
NHMRC	National Health and Medical Research Council
NMU	Nonmedical use
NMUPO	Nonmedical use of prescription opioids
OST	Opioid substitution therapy
OUD	Opioid use disorder
PO	Prescription opioid
POD	Prescription opioid dependence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk ratio
SDG	Sustainable Development Goal
SE	Standard error
SUD	Substance use disorder
US	United States (of America)
WHO	World Health Organization
WMHS	World Mental Health Survey
YLD	Years Lived with Disability
YLL	Years of Life Lost due to mortality

Executive Summary

Background: Trends in the nonmedical use of prescription opioids (NMUPO) have been rising in the past few decades, causing increases in morbidity and mortality due to prescription opioids (POs). There is some evidence that NMUPO and PO dependence (POD) is correlated to the use of heroin, as well as some evidence that the rise in NMUPO may be linked to the increases in opioid prescribing seen in the past couple of decades. Despite increasing concerns, however, there has been no previous systematic review of the prevalence of POD.

Aims: This study will examine the prevalence of NMUPO and POD globally, with the additional aim of contributing to the Global Burden of Disease (GBD) 2016 study dataset. The objectives of this paper are:

1. To conduct a systematic review of peer-reviewed journal databases to create an updated dataset on the prevalence of global opioid use and dependence.
2. To estimate the global prevalence of POD and to identify the distribution of POD.

Methods: A systematic literature review was performed of the Medline, Embase and PsycINFO databases, and data on the prevalence of illicit and PO nonmedical use and dependence by country were extracted. For countries with data on prevalence of NMUPOs, but with no data on dependence, the prevalence of POD was calculated using the meta-analysis cross-walk adjustment method employed by the GBD study. To do this, a ratio between NMUPOs and POD was calculated using data from studies with both parameters available. This ratio was applied to data with only NMUPO prevalence available, and used to obtain POD prevalence data. All known and imputed POD prevalence data was then used to extrapolate and map regional and super-regional estimates of POD prevalence, weighted on population sizes.

Results: The search resulted in 61376 citations. After title and abstract screening, there were 32 studies from which data was extracted and included in this review. The United States (US) had the most data available on POs, with more than half the data available from this country. The highest prevalence of POD reported was 3.4% from a German study. The meta-analysis resulted in a cross-walk risk ratio (RR) of 0.19 for application to NMUPO prevalence data to obtain estimates of POD prevalence. The region with the highest estimated POD weighted prevalence was Western Europe (3.77%), while the region with the lowest estimate was Australasia (0.89%). The overall super-regional estimate of prevalence of POD for the High Income Super-region (HIS) was 2.43% (1.92 – 3.13%).

Conclusion: This study has found prevalences of POD of up to 3.4% in high-income regions, and these increasing trends are of increasing concern. However, the prevalence of POD is not able to be mapped globally given the current lack of data in many regions of the world. This calls for more research to include POD in their monitor of drug dependence in all regions of the world, as this potentially poses a large burden on the community given its deadly nature. The timely implementation of cost-effective and efficacious prevention and intervention strategies may be able to save much morbidity and mortality.

1. INTRODUCTION

The nonmedical use of prescription opioids (NMUPOs) has been rising globally within the past few decades, particularly in the United States (US) (1), where in 2010, NMUPO was second only to cannabis use (2). There is some evidence of the burden of disease (BOD) posed by the rise of NMUPO (3), but traditional research so far has focused on heroin use and dependence as opposed to prescription opioid (PO) use and dependence (2). NMUPO and PO dependence (POD) have been recognized as potentially serious concerns, with parallel rises in morbidity and mortality due to POs, engendering large socioeconomic burdens. NMUPO cost the US approximately US$53.4 billion in 2006 (3). An increase in opioid prescribing by health practitioners has been linked to rising trends in the NMUPO, which in turn leads to increases in opioid overdose (4). The misuse of prescription medications has been shown to be associated with the misuse of illicit drugs (5), and NMUPO is also thought to lead to opioid dependence and subsequently abuse of illicit substances, such as heroin (6), thereby potentially acting as a “gateway” drug. Despite the rising trends and increasing concerns, however, the prevalences of NMUPO and POD have not previously been systematically elicited on a global level. This paper aims to systematically elucidate the global prevalences of NMUPO and POD. It is hoped that the knowledge gained will help to build a good evidence base from which to better inform prevention and treatment programs in areas of high prevalence.

1.1 Prescription Opioids

POs are a restricted class of analgesic medications used predominantly for the treatment of moderate to severe pain in cancer patients and, increasingly, in non-cancer, chronic pain patients. Opioids are a highly addictive class of substances because of their pleasurable psychological effects via activation of the brain’s reward-pathway, mediated by dopamine in the ventral tegmental area (among others) of the brain (7). However, opioids also have a large number of significant associated harms, even resulting in death due to respiratory depression when taken in large doses, or by opioid-naïve patients.

The NMUPOs occurs when individuals take opioids for the pleasurable side-effects rather than pain relief, and the problems begin when physiological tolerance (the development of neurological compensatory mechanisms to reduce effects on the reward-pathway of the brain) occurs (7). This causes the user to take increasing amounts of POs to gain the same euphoric effect, leading to a dysfunctional need for the substance and the development of PO use disorders and POD (see Methods section for definitions).

1.2 Morbidity and Mortality

The prevalence of POD varies, depending on the study, country and sociodemographic profile of the sample population. Opioid dependence is gaining recognition as a significant cause of morbidity and mortality in various countries around the world, particularly in North America, Eastern Europe and Australia (8). There has been a greater than 30% increase in deaths between 2005 and 2015 globally due to substance use, and mortality analysis of the Global Burden of Disease (GBD) 2015 study shows that more than 70% of all substance use disorder (SUD) deaths were caused by opioids. Opioid

related deaths alone increased by almost a third (29.6%) in the same timeframe, resulting in approximately 122,100 deaths in 2015 (9).

In Europe, Arendt et al (2011) showed that, among those with (SUD), mortality rates were highest for those who used heroin or illegally obtained POs (10), while a study by Casati et al (2012) revealed that opioids were one of the main groups of "misused medications" in Europe (11). In the United States of America (US), among prescription medications, POs are the most commonly misused group according to a subnational study done by Currie et al (2011). This same study showed the prevalence of NMUPOs in the US as 8.2% in 2002 and rising (5). Collaborating authors of the GBD study have also called attention to the increasing mortality in the US due to substance abuse, of which approximately a third is attributable to POs (12). The US Centers for Disease Control and Prevention have named POs as the "fastest growing drug problem" in the US and state that, from 2003, mortality related to POs in the US is greater than mortality due to heroin and cocaine combined (13). Across the border in Canada, NMUPO was 4.8% in 2009 (3) and increasing. Another study revealed that 15.5% of Ontario students used POs non-medically, with 5.9% prevalence in the adult population (2) in more recent years.

Asia – the first and main producer of the original poppy plant from which addictive opium was first derived – is not to be forgotten with regards to opioid use (7). Dargan and Wood (2012) states that more than 50% of "the world's opioid using population lives in Asia" (14). It has previously been difficult to elicit accurate data in Asia, but recent improvements in data collection programs by the United Nations Office of Drugs and Crime have made prevalence estimates more reliable. Dargan and Wood (2012) states that Afghanistan has a 2.7% prevalence of opioid use annually, and is the highest in the world, followed by Iran at 2.3% prevalence. There is as yet no opioid use prevalence data for China and India – two large populations known to use opioids non-medically – leaving large gaps in the current Asian data. There is, however, a study done in Punjab, India, estimating the numbers of opioid dependent people within the Indian state, using respondent driven sampling of opioid dependent persons and a multiplier method (15). The study is not as robust as may be desired, however, and no final estimate of opioid dependence, as a percentage of the population, is given in the paper. An estimate of 232,856 opioid dependent individuals within the state is quoted as the result of the study.

1.3 Socio-demographics

Sociodemographic characteristics of PO users also vary and may be associated with risk of NMUPO and POD. A study by Shield et al (2013) revealed a significant association between NMUPO and age (3): younger people were more likely to engage in NMUPO than those in older age groups. Di Bona et al (2014) showed differing rates of substance use risk behaviours in a study of school students, dependent on race, gender and age, with males and older students being more likely to engage in illicit substance use (16). Benavides et al (2013) revealed that unemployment increased the risk of illicit substance use (17). Currie et al (2011) showed that disabled status is a strong predictor of prescription medication misuse, likely due to the higher numbers of medications usually prescribed to this population. This study also showed that the odds of misuse increased for adults with "student" status or a high school diploma, compared to those with a university degree (5). It was theorized that university students may use POs as a way to relieve stress, and that those with tertiary qualifications were more likely to see a doctor and request treatment. A school-based study found rural students at higher risk of substance use (particularly NMUPO) compared to those in urban areas (18). Interestingly, some studies have found that "married" status (ie. being married) decreases risk of substance use (19-22).

1.4 Effect of Harm Reduction

One of the more serious concerns of NMUPO is its significant correlation to heroin use, demonstrated by Ihongbe and Masho (2016) (6). The same study also showed that the odds of using heroin were highest in the NMUPO group. The high burden placed on society by heroin use and dependence is not to be underestimated, and the timely implementation of harm reduction strategies in the form of prevention and treatment programs can prevent much suffering and even death. The collaborating authors of the GBD have noted that there is an "inverse pattern" between the intensity of harm reduction strategies and excess mortality (12). Australia, which has the highest number of and "most intense" interventions (eg. opioid substitution therapy (OST) and needle exchange programs), also has the lowest excess mortality due to opioid overdose. Eastern European countries with high prevalence have few interventions and high excess mortality. A study by Degenhardt et al (2011) showed that users not in treatment had a higher mortality risk than those in current treatment (23). Therefore, the benefits of intervention programs are significant and multiple, and should be implemented in areas where there are high burdens of illicit opioid use, NMUPO and POD.

1.5 Global Burden of Disease Study and the Sustainable Development Goals

The Global Burden of Disease (GBD) study is the most comprehensive worldwide epidemiological study on 315 diseases and injuries. It is an ongoing, international, observational study depicting the morbidity and mortality of numerous communicable and non-communicable diseases across many nations, and generating comparable data with the use of standardised tools (8, 24). The study estimates disease burden with the use of a combination of years of life lost (YLL) and years lived with disability (YLD), known as the disability adjusted life year (DALY). The measure of the DALY was developed in conjunction with the World Bank in the 1990s, and is a means of combining the health and economic effects of diseases (25). Analysis of the GBD 2015 study found that both total DALY's and age-standardised DALY rates due to opioid use disorders (OUD) increased substantially between 1990 and 2015, with OUD named a "growing health threat" by international experts in the field (8). However, the GBD 2015 study results for OUDs are heavily focused on heroin dependence, as this has had a higher burden of disease historically. There remains no systematic data on the prevalence of POD across the world.

The estimation of disease burden via DALYs caused mental disorders, including substance dependence, to gain recognition as a significant cause of economic and social loss. This recognition of mental health disease as a significant problem globally resulted in the inclusion of substance dependence into the Sustainable Development Goals (SDGs) 2015 (12, 24). Goal 3, target 3.5 states "strengthen the prevention and treatment of substance abuse, **including narcotic drug abuse** and harmful use of alcohol" (emphasis added) (24), with specific indicators for intervention needs. This recognition and incorporation into the international SDGs acknowledges that there is an urgent need for effective, cost-efficient interventions and – in conjunction with this – a good understanding of where the BOD of substance dependence lies globally. Much of the current data on opioid use is focused on illicit use, ie. heroin use. However, there is a lack of systematic research conducted on NMUPO and POD to date. The intent of this project is to help fill in the present gap in epidemiological knowledge by mapping the prevalence of POD globally, thereby contributing to the development of evidence-based programs and interventions.

1.6 Aims and Rationale

Eliciting and presenting the prevalence and patterns of POD globally enables an estimation of its harms, as well as the BOD associated with NMUPO and POD, which has effects at individual and community levels: psychologically, physiologically, socially and economically. An estimation of disease burden can increase the evidence base to aid in the development of preventative policies, strategies and programs, at national and local levels, to decrease the prevalence of NMUPO and POD (12).

This study will examine the prevalence of NMUPO and POD globally, with the additional aim of contributing to the GBD 2016 study dataset. The objectives of this paper are:

1. To conduct a systematic review of peer-reviewed journal databases to create an updated dataset on the prevalence of global opioid use and dependence
2. To estimate the global prevalence of POD and to identify its distribution.

2. METHODS

2.1 Systematic Literature Search

Ethics approval for this systematic review was gained from the University of Queensland, School of Public Health Ethics Committee. Multiple research strategies were utilised, including systematic searches of peer-reviewed literature and collaboration with experts in the field. The choice of databases was selected in concert with expert opinion as well as discussion with research librarians. A systematic search of peer-reviewed literature was performed using Medline, Embase and PsycINFO databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) style was employed (26).

The search for this study was undertaken as a part of the GBD 2016 study on the global prevalence of substance dependence, namely cannabis, opioids, cocaine and amphetamines. Only papers pertaining to opioids were selected for the present study. Search terms were grouped into: 1. substances; 2. use or dependence; 3. database specific terms representing substance dependence (eg. MeSH or Emtree terms); and 4. epidemiology measures (eg. prevalence). Search strategy was grouped as ((1 AND 2) OR 3) AND 4. As this search was part of a larger study, total search strings were quite extensive and included terms for all substances in the GBD 2016 study. The search strings for the database searchers are presented in Appendix 6.1.

Epidemiological search strings were standardised according to those used for the Psychiatric Epidemiology and Burden of Disease Group (PEABOD team), of which the researchers were a part. This team researches mental and substance use disorders in the GBD study. Search limitations comprise publication year from 2009 onwards (as the last systematic review on opioid dependence was conducted in 2009), peer reviewed journal articles and human studies. There were no limits set on language as the research team included translators. All stages of screening were performed by two reviewers. Data

extraction was conducted simultaneously with full-screen review ie. if an article was selected for inclusion, the data was immediately extracted.

2.2 Case Definition

NMUPO was defined as any use of POs within the past year that did not follow a doctor's instructions. Each study defined NMUPO slightly differently, but most adhered to some variation of the above. POD was defined according to the Diagnostic and Statistical Manual (DSM) –IV, DSM-IV TR, DSM 5 or International Classification of Disease (ICD) criteria for opioid dependence or OUD.

The DSM-IV TR criteria for substance dependence is a "maladaptive pattern of substance abuse, leading to significant impairment or distress". Within a 12 month period, this must be experienced in conjunction with a minimum of three of the following:

- Tolerance – markedly larger amounts of substance necessary for desired effect OR markedly smaller effect with use of same amount of substance
- Withdrawal – presence of typical withdrawal syndrome for the substance OR substance (or similar substance) taken to reduce/avoid withdrawal symptoms
- regular increase in amount of substance used or duration of use
- unable to control substance use even when willing
- much time spent in obtaining or using substance
- time for other important activities is cut down
- substance use continued even in the knowledge of persistent physical or psychological problems due to use

These criteria were used to ensure standardisation, comparability and consistency across all selected studies.

2.3 Study Selection and Bias

The inclusion criteria for this analysis were: utilisation of DSM or ICD criteria (as discussed above) for definition of dependence to ensure comparability and quality of data, recall period not more than one year (ie. NMUPO or POD in past year), studies with samples that were representative of the general population to decrease bias (eg. hospital data, prison or university samples excluded), sufficiently detailed methods section to allow assessment of study quality, and data not already captured by another paper already included in the study. Relevant school-based studies were included, given the sparsity of general population studies that include individuals under the age of eighteen years.

Recall period was maintained at one year or less to ensure accuracy of results, as it has been shown that "lifetime" recall of sample populations may be biased (27). Studies that presented data obtained from non-representative sample populations, such as treatment groups, prison inmates, hospital patients, university students etc, were excluded, as prevalence estimates from these samples are likely to be over-estimates compared to the general population, and present the risk of bias. The number of those using POs non-medically, or who are opioid dependent, is likely to be falsely elevated (such as in treatment groups) or falsely depressed in these samples. Students at university often have a different

demographic profile to the general population. For this reason, studies including sample populations from these or similar groups, which were not deemed to accurately represent the general population of that country/area, were excluded. Due to these strict criteria, as well as to the definitions of nonmedical use (NMU) and dependence used, study results are comparable and the risk of bias within and across individual studies has been minimised.

2.4 Data Extraction

Data was extracted according to the Institute for Health Metrics and Evaluation (IHME) data extraction sheet for the GBD datasets. Data variables of interest included drug type, use or dependence, country, population representativeness, study details (eg. year, type), sample population demographics, and relevant statistics (eg. sample size, prevalence, confidence intervals, standard error). For this paper, only studies focusing on the prevalence of opioid NMU, opioid dependence, NMUPO and POD were selected for analysis.

2.5 Level of Recommendation of Included Studies

The National Health and Medical Research Council (NHMRC) of Australia “Grades of Recommendation” (28) was used to classify the studies selected in this paper (see Table 1). The levels of recommendation assigned to different types of sources were as follows:

A: peer-reviewed published literature with strong evidence base and rigorous methods eg. Journal articles

B: non-peer-reviewed trusted sources eg. Reports from internationally-recognised or intergovernmental agency reports eg. UN or WHO reports, government reports

C: conference abstracts, technical reports

D: seminars, presentations, opinion, non-peer-reviewed research with unclear methods

Table 1: Definition of NHMRC Grades of Recommendations

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

2.6 Data Analysis

Data were analysed using Excel and MetaXL packages; MetaXL is an add-in to Excel that supports all major meta-analysis methods. The GBD study presents *dependence* data for all relevant substances. Therefore, the aim of this analysis was to estimate POD globally.

2.6.1 Study Characteristics, Descriptive Statistics and Data Availability

First it is necessary to examine the data that is available for prevalence of opioid and heroin use and dependence in each country. All prevalence data for all opioid types in each study were extracted per country location. This data will contribute to the GBD 2016 opioid dependence dataset. Location identification was based on the GBD 2015 population datasets (29). Countries and territories were each given a level identification of "3". Countries/territories were grouped into regions, which were designated as level "2". These regions were then grouped into super-regions and given a level "1" identification (See Appendix 6.2).

2.6.2 Estimating a Cross-walk Ratio from Nonmedical Use to Dependence for Prescription Opioids

The aim of this study is to estimate the global prevalence of POD. However, there may be some countries that only have data on NMUPO. Therefore, it may be necessary to estimate dependence data from NMU only data. For this paper, POD estimates will be calculated using the cross-walk method utilised by the GBD study (12). This method employs a cross-walk meta-analysis to obtain a ratio between NMU and dependence from original data containing both variables. This ratio will then be applied to data that has only NMU data available.

Studies with data for both PO NMU and dependence were used for the cross-walk meta-analysis using a random effects model forest plot. The standard error of the mean (SE) will be required for these calculations; if a study does not supply the SE, it will be calculated using the standard formula: (SE) = square root (prevalence * (1 – prevalence) / sample size). For the purposes of this analysis, DSM-IV or DSM-5 diagnosed prescription opioid use disorder (POUD) will be placed into the same category as POD. This is consistent with the changes made to DSM-5, which integrates POUD into the diagnosis of PO dependence (30). A risk ratio (RR) with 95% confidence intervals will be estimated for POD compared to NMUPO for each study, then pooled by conducting meta-analyses. Cochrane's Q tests and I^2 index will be used to assess heterogeneity.

2.6.3 Estimation of Prescription Opioid Dependence Based on Data for Prescription Opioid Nonmedical Use

The pooled risk ratio (RR) obtained from the meta-analysis will then be used to "cross-walk" (ie. adjust) *known* NMUPO data to *estimated* POD data for that country. This will be done by applying the calculated RR to NMU data to obtain POD data estimates. The prevalence of POD will be estimated by multiplying the reported PO NMU prevalence with the cross-walk RR. This will be done for studies with data on PO NMU only, and with no data for POD.

2.6.4 Estimation of Regional and Super-Regional Prevalence of Prescription Opioid Dependence

Country estimates (%) of POD will then applied to regional and super-regional locations. These regional and super-regional estimates (%) will be used to calculate estimates of number of population with POD from GBD 2015 country population data.

The estimated regional and super-regional prevalence estimates were the mean of available country-level estimates, within a region or super-region respectively, weighted by estimated country aged 15-64 years United Nations population size. This procedure involves a three-step process. Step one uses available prevalence data within a country to estimate number of cases within the country. In countries with data, this will be estimated by multiplying the prevalence (%) in a given country with the population size of that country. Step two calculates the weighted prevalence of a region. This is done by first obtaining the sum of the estimated number of cases across all countries within the region with available data (calculated from step one). This is then divided by the sum of the population sizes of those countries. Step three uses the weighted prevalence of a region (calculated from step two) to impute the number of cases in countries with no data within that same region, which are summed to estimate the cases in the regions.

These steps will be performed for each of the regions for which POD was estimated. If a region does not have any country with data, this region will be excluded from the above extrapolation process. Super-regional estimates will be extrapolated from regional estimates. The Tableau data visualization package will be used to globally map the population estimates obtained for regional and super-regional locations with data.

3. RESULTS

3.1 Search Results

Systematic database searches returned the following: PsycINFO 12,180 results; Medline 18,930 results and Embase 30,266 results (see Figure 1). A further 17 resources were identified through expert collaboration and hand searches. After removal of duplicates, 46615 articles remained for screening. The number of records excluded in the title screen was 42459. Abstract screen removed a further 3574 papers, with 600 records identified for full-screen review. During full-screen review, papers were excluded if: data was already captured, such as same data already extracted from another paper or study (n = 43), sample was biased and did not meet the sample representativeness inclusion criteria (n = 50), no usable data in the paper (n = 76), no data on opioids use or opioids dependence (n = 327), paper was a commentary or no original empirical data (n = 37), recall period more than one year, e.g. lifetime prevalence (n = 35) (see Figure 1). Due to the inclusion of ALL four drugs (cannabis, cocaine and amphetamines, as well as opioids) relevant to the GBD study during the systematic database search, the search returned a high number of records. Similarly, the high number of records excluded in the full text screen is also due to the exclusion of articles pertaining to one of the other drugs. There was a total of 32 studies included in the final analysis, with eight studies with data on POD and 19 studies on NMUPO.

3.2 Evidence of Nonmedical Use and Dependence from the Systematic Review

A summary of the studies extracted after screening is presented in Table 2. Please see section 2.6.1 above and Appendix 6.2 for explanation of location identification, which is based on the GBD study. There were four studies with data for any opioid NMU, and one study for any opioid dependence. NMUPO had the most data extracted from a total of 19 studies. There were six studies that presented data for both NMUPO and POD, with a further two studies on PO dependence alone. There were two studies with heroin use data, and two studies with heroin dependence data. Eight of the above studies included data from school surveys. NB. The numbers given above are not exclusive of one another and some studies contained more than one type of data.

Table 3 below presents all the data extracted from the included studies. A complete list of the studies in Table 3 can be found in Appendix 6.3. There are a total of 114 data-points extracted from 32 sources. All data presented are for both sexes combined, ie. there is no stratification for sex. This is due to paucity of included studies that have stratified data by sex. The highest prevalence of POD is 3.4% in Germany (Pabst et al, 2013), with the lowest prevalence in the US at 0.2% (Boyd et al, 2009). The highest prevalence of opioid use is in Germany (Pabst et al, 2013) with 61.9% use. However, this value is very high and this “use” is likely use of *any* analgesic/PO, including medical use of POs (31). Therefore, this data-point is excluded from further analysis. The second highest prevalence of NMUPO is in Spain (Aguilar-Palacio et al, 2014) with 23.3%.

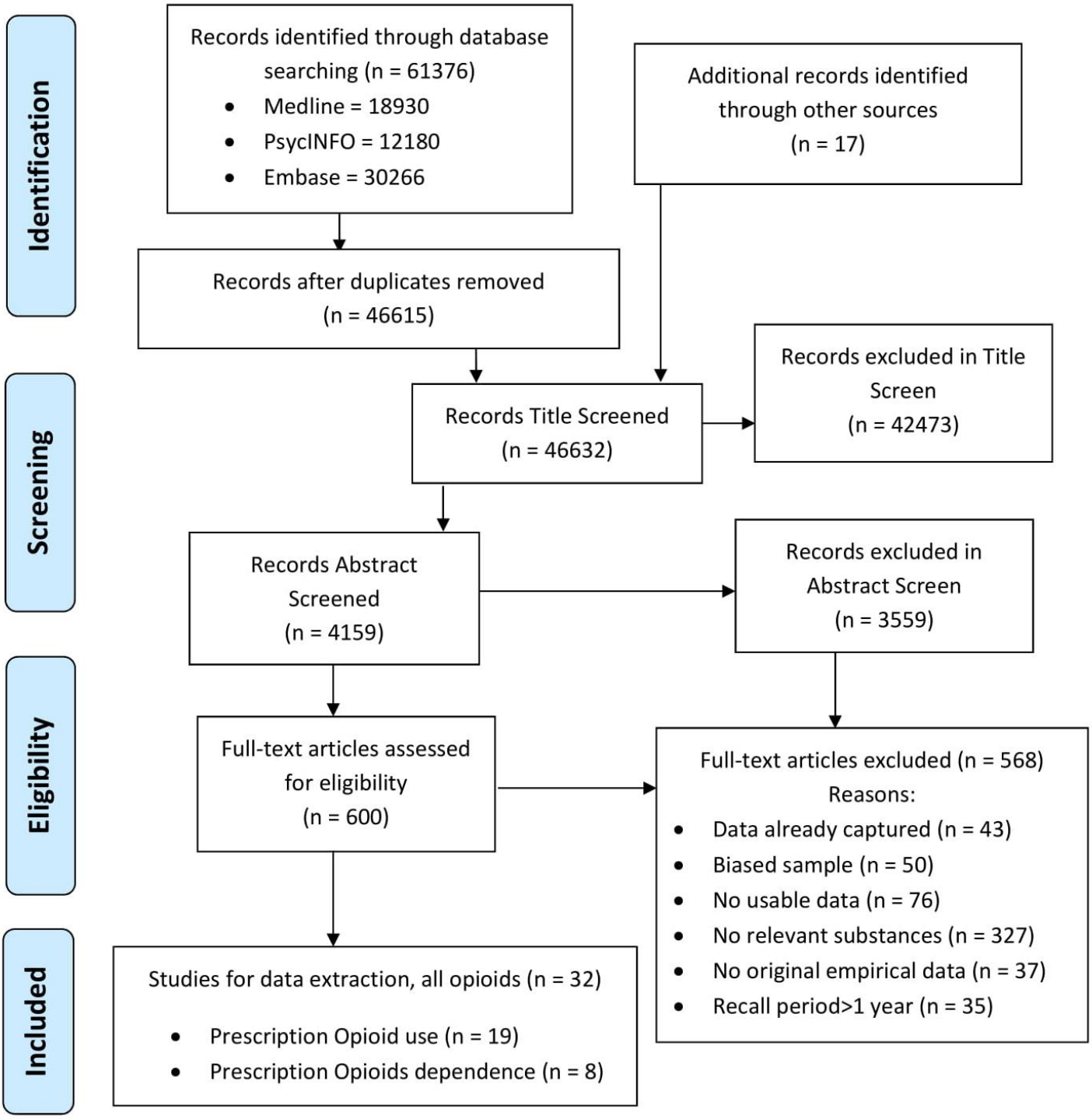

Figure 1: PRISMA Flow Diagram for study inclusion

The third highest prevalence of NMUPO is 15.5% in Canada (Fischer et al, 2013), but it must be noted that this age range is a younger demographic of 15-18 year olds. All extracted NMUPO prevalences around 10% have a younger age group for the sample, and are usually school-based samples. While this is representative for this age range, it is not representative of the general population as a whole, and could skew the results. Therefore, the next highest prevalence of NMUPO selected for a more representative age range (12-99 years) is 7.7% in the US (Back et al, 2010). The lowest prevalence of NMUPO is 0.06% in the US (Jones et al, 2016). It is interesting to note that no studies from the United Kingdom had data for extraction as per the results of this literature search.

As per the classification in Table 1, only two sources had levels of recommendation other than level A: data from the Australian National Drug Strategy Household Survey (NDSHS), which is an Australian government publication (32); and data from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which is the leading drug monitoring agency for the European Union and an inter-governmental, internationally recognised body (33); both of which had a Grade B level of recommendation (28).

Australia only has data for analgesic, buprenorphine and methadone use, available from the NDSHS 2014. The NDSHS estimates any PO use in Australia at 3.8%. Many European countries also have only grade B level of recommendation for data on any opioid use (Czech Republic), opioid dependence (Slovenia, Latvia, Cyprus, France, Germany, Greece, Malta, Norway, Portugal), or heroin dependence (Italy, Spain) from the EMCDDA 2016 (see Table 2).

Egypt is the only country outside of the High Income Super-region to have original NMUPO data available (Bassiony et al, 2015), with a POD prevalence of 0.49%. The Southeast Asia, East Asia, and Oceania Super-region only has data on heroin use in Thailand available (Wongtongkam et al, 2015), while the Latin America and Caribbean, and the South Asia Super-regions, have no opioid use or dependence data available from this systematic literature search. The author is aware, however, that this may merely be due to language barriers and restriction to peer-reviewed databases (see Limitations section).

3.3 Cross-walk Meta-Analysis Using Studies with Prescription Opioid Nonmedical Use and Dependence Data

The most data extracted was for NMUPO (see Table 2 below). However, this project focuses on POD. Therefore, POD data were estimated from NMUPO data, so as to make use of all available data. For this purpose, a cross-walk meta-analysis was performed using studies that presented data on both NMU and dependence for POs. This analysis determined a ratio between NMUPO and POD, which was then used to convert NMUPO to POD for studies that only presented NMUPO data. The series of meta-analyses conducted are presented below, with reasons for arrival at the final cross-walk ratio.

As shown in Table 2, there were only six studies within inclusion criteria that had data for both NMU and dependence of POs – Pabst et al, 2013, Back et al, 2010, Bassiony et al, 2015, Han et al, 2015, Martins et al, 2010 and Saha et al, 2016. The data from Pabst et al, 2013, however, appears too high for NMUPO (61.9%), and is more likely to be *any* use of POs

and other analgesics, including approved medical use (31). This study was therefore excluded from the analysis as it would likely yield invalid results.

Figure 2 below shows the forest plot meta-analysis of the remaining five studies (see Appendix 6.4, Table 7 for complete statistics). However, data from Bassiony et al, 2015 appears to be an extreme outlier with a small sample size (n = 204) and corresponding low numbers for data values of interest (PO use = 18, PO dependence = 1). This study was therefore excluded from analysis, as it was deemed to be an outlier.

Figure 3 below shows the forest plot of the meta-analysis after removal of the data from Bassiony et al, 2015. There are only four studies, but fourteen data points. The Han et al, 2015 study reported data across multiple years and dominates the results of the meta-analysis (see Appendix 6.4 for complete statistics). Therefore, only the most recent data from Han et al, 2015 was used for analysis, leaving just four data points for analysis.

Finally, Figure 4 below is a forest plot of the analysis of the four remaining eligible studies with only the most recent data from Han et al, 2015. The Cochrane's Q chi-squared test showed statistically significant results, $Q=62.12$, $p<0.001$, with considerable heterogeneity, $I^2=95\%$. Therefore, a random effects model was utilized. The pooled risk ratio (RR), or overall RR, obtained is 0.19 (0.14 – 0.25; see Appendix 6.4 for complete statistics). This result was used in the estimation of POD from existing NMUPO data for the cross-walk (see Table 4).

Table 2: Studies by Type of Opioid Use

Opioid Use Type	Study Name
Any Opioid Nonmedical Use	Peltzer 2010, Zuccato 2016, Lawental 2015, EMCDDA 2016: Czech Republic
Any Opioid Dependence	EMCDDA 2016: Slovenia, Latvia, Cyprus, France, Germany, Greece, Malta, Norway, Portugal
Prescription Opioid Nonmedical Use	Currie 2011, Currie 2012, Schepis 2016, Moore 2009, Biondo 2014, Arterberry 2016, Aguilar-Palacio 2014, Ihongbe 2016, Fischer 2013, Shield 2011, Shield 2013a, Shield 2013b, Brands 2010, Fiellin 2013, McCabe 2013, Jones 2016, Kerridge 2015, Fischer 2010, Catalano 2011
Prescription Opioid Dependence	Boyd 2009, Kraus 2013
Prescription Opioid Nonmedical Use and Dependence	Han 2015, Bassiony 2015, Martins 2010, Pabst 2013, Saha 2016, Back 2010
Heroin Use	Wongtongkam 2015, Ihongbe 2016
Heroin Dependence	Sopko 2016, EMCDDA 2016: Italy, Spain

Table 3: Opioid Use, Nonmedical Use and Dependence per Super-region (1), Region (2) and Country / Territory (3): All Extracted Data. Male and Female Combined

								USE				DEPENDENCE			
#	Location[#]	First Author (year)	Data (Y)	Age (Year)	School Survey	LOR	Type (O)	%	N	Cases	SE	Type (O)	%	N	Cases	SE
1	SOUTHEAST ASIA, EAST ASIA, AND OCEANIA															
2	East Asia			nd												
2	Southeast Asia															
3	Thailand	Wongtongkam (2015)	2011	16-18	Yes	A	H	1.52%	1778	27	0.41%					
2	Oceania			nd												
1	CENTRAL EUROPE, EASTERN EUROPE, AND CENTRAL ASIA															
2	Central Asia			nd												
2	Central Europe															
3	Czech Republic	EMCDDA (2016)			No	B	H, M, B	<0.01%		11300						
3	Czech Republic	Sopko (2016)	2011	15-65	No	A						H	0.21%	6786	14	0.08%
3	Slovenia	EMCDDA (2016)	2013		No	B						H, M, B, O, OST	<0.01%		5200	
2	Eastern Europe															
3	Latvia	EMCDDA (2016)	2014		No	B						O (TD)	<0.01%		6151	
1	HIGH INCOME															
2	High-income Asia Pacific			nd												
2	Australasia															
3	Australia	NDSHS (2014)	2013	12-99	No	B	An, B, M	3.80%	23855	906						
2	Western Europe															
3	Cyprus	EMCDDA (2016)	2014		No	B						H, M, O	0.18%		1094	

												(TD). OST					
3	France	EMCDDA (2016)	2013-2014		No	B						H, M, B, O (TD)	<0.01%		211000		
3	Germany	Kraus (2013)	2000	18-59	No	A						PO	2.25%	8139	183		
3	Germany	Pabst (2013)	2012-2012	18-64	No	A	O (not H)	61.90%	9018	5582	0.01%	PO	3.40%	9054	308	0.003	
3	Germany	Pabst (2013)	2012-2012	18-64	No	A	H	0.20%	9063	18	0.07%						
3	Germany	EMCDDA (2016)	2012		No	B						H, M, B, O	0.30%		155994		
3	Greece	EMCDDA (2016)	2014		No	B						H, OST	<0.01%		17245		
3	Israel	Lawental (2015)	2012-2013	18-40	No	A	M	0.80%	1200	9							
3	Israel	Lawental (2015)	2012-2013	18-40	No	A	O	0.50%	1200	6							
3	Israel	Lawental (2015)	2012-2013	18-40	No	A	H	0.40%	1200	5							
3	Italy	Zuccato (2016)	2010	15-64	No	A	O	0.17%	12323	21	0.07%						
3	Italy	Zuccato (2016)	2012	15-64	No	A	O	0.08%	19294	15	0.04%						
3	Italy	Zuccato (2016)	2014	15-64	No	A	O	0.10%	8465	8	0.07%						
3	Italy	EMCDDA (2016)	2014		No	B						H	<0.01%		203000		
3	Malta	EMCDDA (2016)	2014		No	B						O	<0.01%		1614		
3	Norway	EMCDDA (2016)	2013		No	B						H, M, O	<0.00%		9015		
3	Portugal	EMCDDA (2016)	2012		No	B						O	<0.01%		31858		
3	Spain	EMCDDA (2016)	2013		No	B						H	<0.01%		65648		
3	Spain	Aguilar-Palacio (2014)	2006-2006	16-65	No	A	An	23.30%	993	231							
2	Southern Latin America			nd													

2	High-income North America															
3	Canada	Currie (2011)	2002	18-99	No	A	PO	4.90%	3511	172						
3	Canada	Currie (2011)	2002	18-99	No	A	H	0.10%	3511	3						
3	Canada	Fischer (2013)	2011	15-18	Yes	A	NMUPO	15.50%	3339	518						
3	Canada	Fischer (2013)	2011	18-99	No	A	NMUPO	5.9%	4023	237						
3	Canada	Shield (2011)	2008-2009	18-99	No	A	NMUPO	1.95%	2030	40						
3	Canada	Shield (2013b)	2009	15-99	No	A	NMUPO	4.80%	13082	628						
3	Canada	Fischer (2010)	2008	15-99	No	A	NMUPO	0.50%	16672	83						
3	Canada	Shield (2013a)	2008-2009	18-99	No	A	NMUPO	2.00%	2017	40						
3	Canada	Shield (2013a)	2010	18-99	No	A	NMUPO	7.70%	2015	143						
3	Canada	Currie (2012)	2008-2009	12-18	Yes	A	An	4.00%	45163	1807						
3	Canada	Brands (2010)	2007	12-19	Yes	A	NMUPO	6.20%	2914	181						
3	US	Martins (2010)	2001-2002	18-57	No	A	NMUPO	1.57%	31397	494		POUD	0.40%	31397	127	
3	US	Fiellin (2013)	2006-2008	18-25	No	A	NMUPO	11.76%	55215	6496						
3	US	Saha (2016)	2012-2013	18-99	No	A	NMUPO	4.10%	36309	1579	0.16	POUD	0.89%	36309	330	0.05
3	US	McCabe (2013)	2009-2011	12-18	Yes	A	NMUPO	7.00%	1928	135						
3	US	Han (2015)	2003	18-99	No	A	NMUPO	5.40%	42700	2306		POUD	0.60%	42700	256	
3	US	Han (2015)	2004	18-99	No	A	NMUPO	5.10%	43100	2198		POUD	0.60%	43100	259	
3	US	Han (2015)	2005	18-99	No	A	NMUPO	5.40%	43300	2338		POUD	0.70%	43300	303	
3	US	Han (2015)	2006	18-99	No	A	NMUPO	5.80%	42100	2442		POUD	0.70%	42100	295	
3	US	Han (2015)	2007	18-99	No	A	NMUPO	5.70%	42700	2434		POUD	0.80%	42700	342	

3	US	Han (2015)	2008	18-99	No	A	NMUPO	5.30%	43200	2290		POUD	0.80%	43200	346	
3	US	Han (2015)	2009	18-99	No	A	NMUPO	5.60%	43000	2408		POUD	0.90%	43000	387	
3	US	Han (2015)	2010	18-99	No	A	NMUPO	5.50%	43300	2382		POUD	0.90%	43300	390	
3	US	Han (2015)	2011	18-99	No	A	NMUPO	4.90%	43600	2136		POUD	0.80%	43600	349	
3	US	Han (2015)	2012	18-99	No	A	NMUPO	5.60%	42900	2402		POUD	1.00%	42900	429	
3	US	Han (2015)	2013	18-99	No	A	NMUPO	4.90%	42400	2078		POUD	0.90%	42400	382	
3	US	Jones (2016)	2006	12-99	No	A	NOU	0.50%	67500	338	0.04					
3	US	Jones (2016)	2007	12-99	No	A	NOU	0.60%	67400	404	0.04					
3	US	Jones (2016)	2008	12-99	No	A	NOU	0.06%	67900	41	0.04					
3	US	Jones (2016)	2009	12-99	No	A	NOU	0.70%	68000	476	0.04					
3	US	Jones (2016)	2010	12-99	No	A	NOU	0.70%	67800	475	0.05					
3	US	Jones (2016)	2011	12-99	No	A	NOU	0.60%	70100	421	0.04					
3	US	Jones (2016)	2012	12-99	No	A	NOU	0.60%	68300	410	0.04					
3	US	Jones (2016)	2013	12-99	No	A	NOU	0.50%	67800	339	0.05					
3	US	Schepis (2016)	2002-2003	50-99	No	A	NMPDU	1.00%	9793	98						
3	US	Schepis (2016)	2012-2013	50-99	No	A	NMPDU	1.70%	12696	216						
3	US	Moore (2009)	2001-2002	65-99	No	A	NMUPO	0.50%	7964	40						
3	US	Kerridge (2015)	2012-2013	18-99	No	A						POUD	0.90%	36667	330	
3	US	Catalano (2011)	2003-2004	15-17	Yes	A	NMUPO	12.30%	846	104						
3	US	Back (2010)	2006	12-99	No	A	PO	7.74%	55279	4281		POUD	1.03%	55279	568	
3	US	Boyd (2009)	2004-2005	18-99	No	A						PO	0.20%	33158	62	<0.1%

3	US	Biondo (2014)	2005	17-19	Yes	A	NMUPO	9.00%	15127	1361				
3	US	Biondo (2014)	2006	17-19	Yes	A	NMUPO	9.00%	15127	1361				
3	US	Biondo (2014)	2007	17-19	Yes	A	NMUPO	9.20%	15127	1392				
3	US	Biondo (2014)	2008	17-19	Yes	A	NMUPO	9.10%	15127	1377				
3	US	Biondo (2014)	2009	17-19	Yes	A	NMUPO	9.20%	15127	1392				
3	US	Biondo (2014)	2010	17-19	Yes	A	NMUPO	8.70%	15127	1316				
3	US	Biondo (2014)	2005	17-19	No	A	NMUPO	12.50%	3020	378				
3	US	Biondo (2014)	2006	17-19	No	A	NMUPO	12.80%	3020	387				
3	US	Biondo (2014)	2007	17-19	No	A	NMUPO	10.10%	3020	305				
3	US	Biondo (2014)	2008	17-19	No	A	NMUPO	12.80%	3020	387				
3	US	Biondo (2014)	2009	17-19	No	A	NMUPO	10.80%	3020	326				
3	US	Biondo (2014)	2010	17-19	No	A	NMUPO	9.80%	3020	296				
3	US	Arterberry (2016)	2001-2005	18-99	No	A	NMUPO	1.58%	34,649	547				
3	US	Ihongbe (2016)	2011-2013	18-25	No	A	H	0.73%	55,940	408				
3	US	Ihongbe (2016)	2011-2013	18-25	No	A	O	9.60%	55940	5370				
1	LATIN AMERICA AND CARIBBEAN													
2	Caribbean			nd										
2	Andean Latin America			nd										
2	Central Latin America			nd										
2	Tropical Latin America			nd										
1	NORTH AFRICA AND MIDDLE EAST													
2	North Africa and Middle East													
3	Egypt	Bassiony (2015)	2013	12-17	Yes	A	PO	8.80%	204	18	PO	0.49%	204	1

1	SOUTH ASIA									
2	South Asia			nd						
1	SUB-SAHARAN AFRICA									
2	Central Sub-Saharan Africa			nd						
2	Eastern Sub-Saharan Africa			nd						
2	Southern Sub-Saharan Africa									
3	South Africa	Peltzer (2010)	2008	15-99	No	A	O	0.50%	13828	69
2	Western Sub-Saharan Africa			nd						

# Location identification as per GBD (2015). 1 = Super-region, 2 = Region, 3 = Country / Territory
N = Sample Size, SE = Standard Error, nd = no data, Y = year
LOR = Level of Recommendation
A = peer reviewed journal article. B = Published book / international governmental monitoring organisation report / government report
O = Opioids, PO = Prescription Opioids, H = Heroin, M = Methadone, B = Buprenorphine, An = Analgesics, C = Codeine
OST = opioid substitution therapy, (TD) = Treatment Data
NMUPO = Nonmedical Use of Prescription Opioids, NOU = Nonmedical Oxycontin Use
NMPDU = Nonmedical Prescription Drug Use, POUD = Prescription opioid use disorder
EMCDDA = European Monitoring Centre for Drugs and Drug Addiction, NDSHS = National Drug Strategy Household Survey
NESARC = National Epidemiologic Survey of Alcohol and Related Conditions Waves I and II, NESARC III = NESARC Wave III
OHDUHS = Ontario Student Drug Use and Health Survey, CAMH = Centre for Addiction and Mental Health, NSDUH = National Survey on Drug Use and Health
CADUMS= Canadian Alcohol and Drug Use Monitoring Survey, YSS = Youth Smoking Survey, SSLS = Secondary Student Life Survey
RHC = Raising Healthy Children, MTF = Monitoring the Future
SABSSM = South African National HIV Incidence, Prevalence, Behaviour and Communication Survey

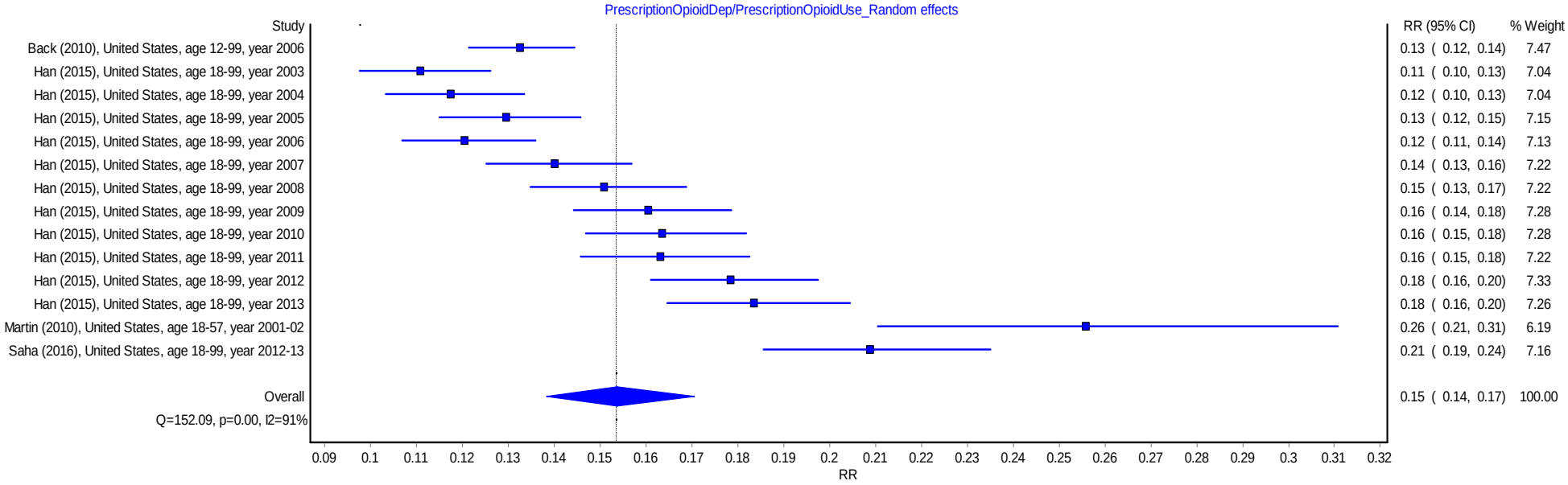

Figure 2: Meta-Analysis All Studies with Nonmedical Use and Dependence Data (Pabst 2013 Excluded)

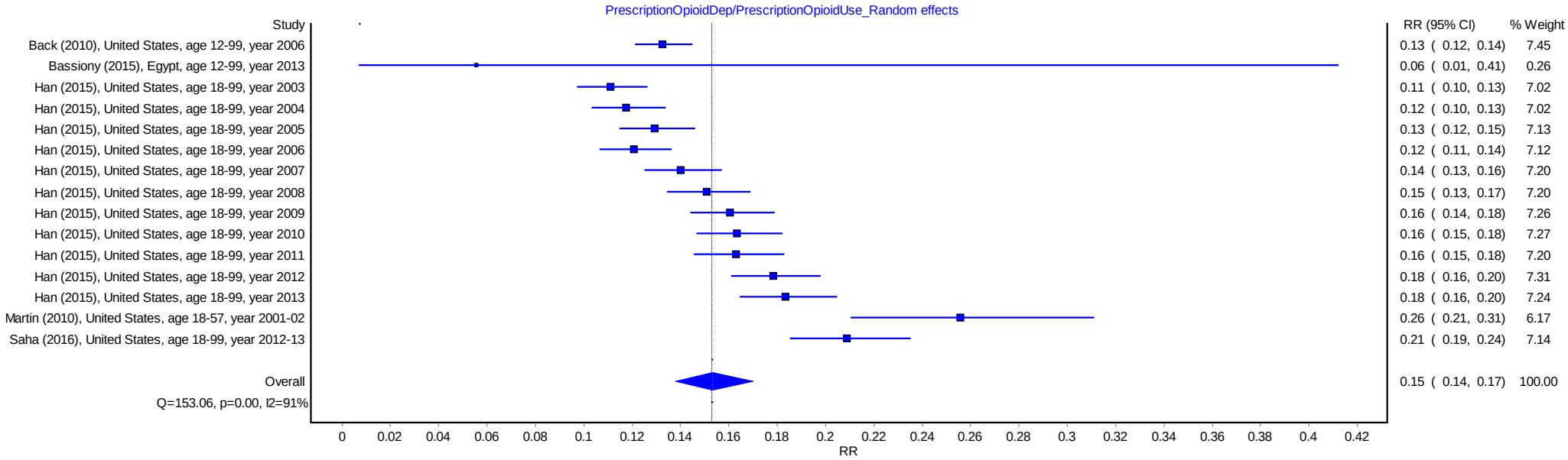

Figure 3: Meta-Analysis Without Egyptian Study (Bassiony, 2015) Data

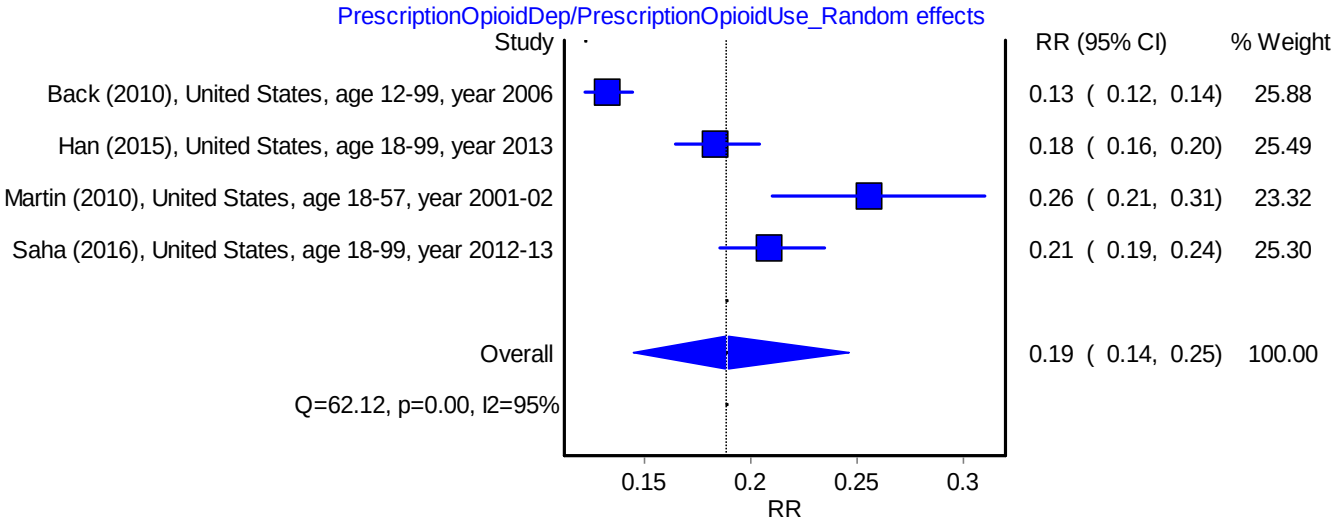

Figure 4: Meta-Analysis with Only Most Recent Data from Han (2015) Study

3.4 Application of the Cross-walk Results to Estimate Prevalence of Prescription Opioid Dependence.

Using the pooled RR from the random effects model meta-analysis above (see Figure 4), NMUPO data are "cross-walked" to POD estimates, i.e. POD data are calculated using NMUPO data. Upper and lower 95% confidence intervals (CIs) are also calculated and shown. To present all data available on POD, all original POD / POUD data and calculated 95% CIs are presented in Table 4 below, as well as all estimated POD data from NMUPO data using the pooled RR of 0.19. Data from the EMCDDA study is not presented for further analysis because much of the data comes from treatment populations and there is insufficient detail on the methods of data collection available (33).

The highest estimate of POD is 4.39% in Spain (Aguilar-Palacio et al, 2014). The lowest estimate is 0.01% in the US (Jones et al, 2016). The US has fifteen studies with original or estimated dependence data, with Canada following with eight studies. Australia, Germany, Spain and Egypt each have one study included in the cross-walk application.

For each country with data, one original data-point was chosen as the most representative POD estimate for that country, shown with an asterisk (*) in Table 4 below. This was the data value used for that country when mapping the prevalence of POD. Australia, Germany and Spain each had one study with one data-point. The data-point chosen for Canada from Fischer et al, 2013 was because this was the most recent data available for Canada (collected 2011), with the most representative age group (18 – 99 years). The data-point chosen for the US from Han et al, 2015 was also because this was one of the most recent data-points available (collected 2013), with the most representative age range (18 – 99 years), and because it had the largest sample size given its demographics. Egypt was not mapped as this was the only country that did not lie within the High Income Super-region.

Table 4: Extracted Data for Opioid Dependence, Plus Data Cross-Walked to Opioid Dependence per Super-region (1), Region (2) and Country / Territory (3)

Level	Location	First Author (Year)	Year of Data Collection	Definition	%	Lower	Upper
1	Southeast Asia, East Asia, and Oceania				nd		
2	East Asia				nd		
2	Southeast Asia				nd		
2	Oceania				nd		
1	Central Europe, Eastern Europe, and Central Asia				nd		
2	Central Asia				nd		
2	Central Europe				nd		
2	Eastern Europe				nd		
1	High-income						
2	High-income Asia Pacific						
2	Australasia						
3	Australia	NDSHS (2013)*	2013	An, B, M, O use: cross-walked to dependence	0.72%	0.58%	0.88%
2	Western Europe				0.886%	0.736%	1.066%
3	Germany	Pabst (2013)*	2012	NMPD dependence	3.40%	2.92%	3.95%
3	Spain	Aguilar-Palacio (2014)*	2006	An use: cross-walked to dependence	4.39%	2.94%	6.51%
2	Southern Latin America				nd		
2	High-income North America						
3	Canada	Currie (2011)	2002	NMUPO: cross-walked to dependence	0.92%	0.58%	1.47%
3	Canada	Fischer (2013)	2011	NMUPO: cross-walked to dependence	2.92%	2.23%	3.82%
3	Canada	Fischer (2013)	2011	NMUPO: cross-walked to dependence	1.11%	0.75%	1.66%
3	Canada	Shield (2011)	2008-2009	NMUPO: cross-walked to dependence	0.37%	0.14%	0.95%
3	Canada	Shield (2013b)	2009	NMUPO: cross-walked to dependence	0.90%	0.71%	1.16%
3	Canada	Fischer (2010)	2008	NMUPO cross-walked to dependence	0.09%	0.05%	0.18%

3	Canada	Shield (2013a)	2008-2009	NMUPO: cross-walked to dependence	0.38%	0.15%	0.97%
3	Canada	Shield (2013a)*	2010	NMUPO: cross-walked to dependence	1.45%	0.89%	2.37%
3	Canada	Currie (2012)	2008-2009	NMPD use: cross-walked to dependence	0.75%	0.65%	0.87%
3	Canada	Brands (2010)	2007	NMUPO: cross-walked to dependence	1.17%	0.74%	1.84%
3	US	Martins (2010)	2001-2002	POU disorder	0.40%	0.31%	0.51%
3	US	Fiellin (2013)	2006-2008	POU: cross-walked to dependence	2.22%	2.05%	2.39%
3	US	Saha (2016)	2012-2013	POU Disorder	0.89%	0.77%	1.03%
3	US	McCabe (2013)	2009-2011	POU: cross-walked to dependence	1.32%	0.78%	2.23%
3	US	Han (2015)	2003	POU disorder	0.60%	0.51%	0.71%
3	US	Han (2015)	2004	POU disorder	0.60%	0.51%	0.71%
3	US	Han (2015)	2005	POU disorder	0.70%	0.60%	0.82%
3	US	Han (2015)	2006	POU disorder	0.70%	0.60%	0.82%
3	US	Han (2015)	2007	POU disorder	0.80%	0.69%	0.93%
3	US	Han (2015)	2008	POU disorder	0.80%	0.69%	0.92%
3	US	Han (2015)	2009	POU disorder	0.90%	0.79%	1.03%
3	US	Han (2015)	2010	POU disorder	0.90%	0.79%	1.03%
3	US	Han (2015)	2011	POU disorder	0.80%	0.69%	0.92%
3	US	Han (2015)	2012	POU disorder	1.00%	0.88%	1.14%
3	US	Han (2015)*	2013	POU disorder	0.90%	0.78%	1.03%
3	US	Jones (2016)	2006	NOU: cross-walked to dependence	0.09%	0.07%	0.13%
3	US	Jones (2016)	2007	NOU: cross-walked to dependence	0.11%	0.08%	0.15%
3	US	Jones (2016)	2008	NOU: cross-walked to dependence	0.01%	0.00%	0.03%
3	US	Jones (2016)	2009	NOU: cross-walked to dependence	0.13%	0.10%	0.18%
3	US	Jones (2016)	2010	NOU: cross-walked to dependence	0.13%	0.10%	0.18%
3	US	Jones (2016)	2011	NOU: cross-walked to dependence	0.11%	0.08%	0.15%

3	US	Jones (2016)	2012	NOU: cross-walked to dependence	0.11%	0.08%	0.15%
3	US	Jones (2016)	2013	NOU: cross-walked to dependence	0.09%	0.07%	0.13%
3	US	Schepis (2016)	2002-2003	NMPD Use: cross-walked to dependence	0.19%	0.10%	0.35%
3	US	Schepis (2016)	2012-2013	Weighted NMPDU: cross-walked to dependence	0.32%	0.21%	0.49%
3	US	Moore (2009)	2001-2002	NMUPO: cross-walked to dependence	0.09%	0.04%	0.24%
3	US	Kerridge (2015)	2012-2013	POU disorder	0.90%	0.78%	1.04%
3	US	Catalano (2011)	2003-2004	NMUPO: cross-walked to dependence	2.32%	1.28%	4.18%
3	US	Back (2010)	2006	POU disorder	1.03%	0.92%	1.15%
3	US	Boyd (2009)	2004-2005	PO dependence	0.20%	0.14%	0.28%
3	US	Biondo (2014)	2005	NMUPO: cross-walked to dependence	1.70%	1.44%	2.00%
3	US	Biondo (2014)	2006	NMUPO: cross-walked to dependence	1.70%	1.44%	2.00%
3	US	Biondo (2014)	2007	NMUPO: cross-walked to dependence	1.73%	1.47%	2.05%
3	US	Biondo (2014)	2008	NMUPO: cross-walked to dependence	1.72%	1.45%	2.02%
3	US	Biondo (2014)	2009	NMUPO: cross-walked to dependence	1.73%	1.47%	2.05%
3	US	Biondo (2014)	2010	NMUPO: cross-walked to dependence	1.64%	1.38%	1.94%
3	US	Biondo (2014)	2005	NMUPO: cross-walked to dependence	2.36%	1.72%	3.22%
3	US	Biondo (2014)	2006	NMUPO: cross-walked to dependence	2.41%	1.77%	3.29%
3	US	Biondo (2014)	2007	NMUPO: cross-walked to dependence	1.90%	1.34%	2.70%
3	US	Biondo (2014)	2008	NMUPO: cross-walked to dependence	2.41%	1.77%	3.29%
3	US	Biondo (2014)	2009	NMUPO: cross-walked to dependence	2.04%	1.45%	2.85%

3	US	Biondo (2014)	2010	NMUPO: cross-walked to dependence	1.85%	1.29%	2.63%
3	US	Arterberry (2016)	2001-2005	NMUPO: cross-walked to dependence	0.30%	0.23%	0.39%
3	US	Ihongbe (2016)	2011-2013	NMUPO: cross-walked to dependence	1.8%	0.01663	0.01968
1	Latin America and Caribbean				nd		
2	Caribbean				nd		
2	Andean Latin America				nd		
2	Central Latin America				nd		
2	Tropical Latin America				nd		
1	North Africa and Middle East						
2	North Africa and Middle East						
3	Egypt	Bassiony (2015)*	2013	PO dependence	0.49%	0.05%	4.35%
1	South Asia				nd		
2	South Asia				nd		
1	Sub-Saharan Africa				nd		
2	Central Sub-Saharan Africa				nd		
2	Eastern Sub-Saharan Africa				nd		
2	Southern Sub-Saharan Africa				nd		
2	Western Sub-Saharan Africa				nd		

Levels: 1 = Super-region, 2 = Region, 3 = Country / Territory
NDSHS = National Drug Strategy Household Survey
* Data-point chosen as most representative of the population for regional population estimate
US = United States
nd = no data
O = Opioids, PO = Prescription Opioids, H = Heroin, M = Methadone, B = Buprenorphine, An = Analgesics, C = Codeine
NMUPO = Nonmedical Use of Prescription Opioids, NOU = Nonmedical Oxycontin Use, NMPD = Nonmedical Prescription Drug

3.5 Prevalence of Prescription Opioid Dependence

Dependence data were calculated for all countries with NMUPO data. Thereafter, POD estimates (%) were calculated for *all* countries in regions and super-regions that had some data available. The countries with data on POD (original and imputed) were Australia, Germany, Spain, Canada and the US, all of which are in the High Income Super-region. Therefore, it was decided to estimate population numbers of POD only in this High Income Super-region, as it is the only location with an adequate amount of data. For the countries and regions within the High Income Super-region without data, prevalence cases were imputed based on the strategy described in detail in the Methods section.

Table 5 below presents all known and imputed POD estimates per country and region. It is noted that, due to paucity of data, the weighted prevalences for POD were imputed for 29 out of the 34 countries in this super-region. The estimated number of people with POD was 2.9 million in the US, 524,000 in Canada, 215,000 in Australia, 2.8 million in Germany, and 2.1 million in Spain. The original and imputed percentage prevalences of POD in the High Income Super-region are presented graphically in Figure 5 below. The overall prevalence of POD was estimated to be 2.43% (1.92 - 3.13%) in the High Income Super-region. Regional estimations are as follows: High Income Asia Pacific 2.43% (1.92 – 3.13%), Australasia 0.89% (0.74 - 1.07%), Western Europe 3.77% (2.93 – 4.89%), Southern Latin America 2.43% (1.92 – 3.13%) and High Income North America 0.96% (0.79 – 1.17%). The only location with known data not depicted on the map is Egypt (as it is not part of the High Income Super-region), which has an estimated 0.5% (0.1- 4.3 95% CI) prevalence of POD.

The region with the highest POD prevalence estimate is Western Europe (3.77%). Within this region, Spain has the highest country prevalence estimate (4.39%). The region with the lowest POD prevalence estimate is Australasia (0.89%), with Australia and New Zealand having an estimated 215,000 and 40,000 PO dependent people respectively. Overall, the country with the highest number of estimated PO dependent persons is Japan (3.1 million people) and the country with the lowest number is Greenland (516 people). These numbers are, of course, only estimates, and are dependent on the population size of the country.

Table 5: Estimating the Prevalence for Prescription Opioid Dependence in Countries/Territories (3) and Regions (2) of the High-Income Super-Region (3) Using Results from Meta-Analysis

Level	Location	Population**	Calculated Estimate	Estimate %	Lower 95% CI	Higher 95% CI	Estimated Number	Low Number	High Number
1	HIGH-INCOME	1,070,090,763	Super-regional estimation, based on regional estimations	2.43%	1.92%	3.13%	26,052,241	20,527,582	33,474,971
2	High-income Asia Pacific	182,936,134	*Applying super-regional estimate to region*	*2.43%*	*1.92%*	*3.13%*	*4,453,731*	*3,509,269*	*5,722,675*
3	Brunei	423,003	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*10,298*	*8,114*	*13,233*
3	Japan	128,306,399	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*3,123,725*	*2,461,305*	*4,013,728*
3	South Korea	50,283,063	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*1,224,183*	*964,581*	*1,572,973*
3	Singapore	3,923,668	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*95,525*	*75,268*	*122,742*
2	Australasia	28,884,967	Regional estimation from country with known data	0.89%	0.74%	1.07%	255,895	212,698	307,771
3	Australia*	24,321,713	Country with known data	0.89%	0.74%	1.07%	215,468	179,096	259,149
3	New Zealand	4,563,255	*Applying regional estimate to country*	*0.89%*	*0.74%*	*1.07%*	*40,426*	*33,602*	*48,622*
2	Western Europe	433,621,186	Regional estimation from country with known data	3.77%	2.93%	4.89%	16,326,994	12,703,241	21,219,276
3	Andorra	79,452	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*2,992*	*2,328*	*3,888*
3	Austria	8,669,942	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*326,446*	*253,992*	*424,264*
3	Belgium	11,332,642	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*426,704*	*331,998*	*554,563*
3	Cyprus	891,960	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*33,585*	*26,131*	*43,648*
3	Denmark	5,710,725	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*215,024*	*167,300*	*279,455*
3	Finland	5,550,457	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*208,989*	*162,605*	*271,612*

3	France	65,232,014	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*2,456,159*	*1,911,018*	*3,192,132*
3	Germany*	83,628,107	Country with known data	3.40%	2.92%	3.95%	2,843,356	2,443,455	3,306,039
3	Greece	10,921,532	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*411,225*	*319,954*	*534,446*
3	Iceland	326,395	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*12,290*	*9,562*	*15,972*
3	Ireland	4,789,767	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*180,348*	*140,320*	*234,388*
3	Israel	8,049,386	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*303,081*	*235,812*	*393,897*
3	Italy	62,797,397	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*2,364,489*	*1,839,694*	*3,072,994*
3	Luxembourg	556,434	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*20,951*	*16,301*	*27,229*
3	Malta	418,373	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*15,753*	*12,257*	*20,473*
3	Netherlands	17,190,587	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*647,271*	*503,610*	*841,222*
3	Norway	5,164,354	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*194,452*	*151,293*	*252,718*
3	Portugal	10,799,730	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*406,639*	*316,386*	*528,485*
3	Spain*	48,751,005	Country with known data	4.39%	2.94%	6.51%	2,141,071	1,434,685	3,171,940
3	Sweden	9,807,976	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*369,296*	*287,332*	*479,954*
3	Switzerland	8,278,353	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*311,702*	*242,520*	*405,102*
3	United Kingdom	64,243,837	*Applying regional estimate to country*	*3.77%*	*2.93%*	*4.89%*	*2,418,952*	*1,882,069*	*3,143,776*
2	Southern Latin America	64,798,432	*Applying super-regional estimate to region*	*2.43%*	*1.92%*	*3.13%*	*1,577,571*	*1,243,030*	*2,027,048*
3	Argentina	43,413,241	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*1,056,931*	*832,797*	*1,358,069*
3	Chile	17,948,052	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*436,960*	*344,298*	*561,458*
3	Uruguay	3,434,236	*Applying super-regional estimate to country*	*2.43%*	*1.92%*	*3.13%*	*83,609*	*65,879*	*107,431*

2	High-income North America	359,850,051	Regional estimation from country with known data	0.96%	0.79%	1.17%	3,438,050	2,859,344	4,198,201
3	Canada*	36,145,518	Country with known data	1.45%	0.89%	2.37%	524,610	320,629	855,263
3	Greenland	54,024	*Applying regional estimate to country*	*0.96%*	*0.79%*	*1.17%*	*516*	*429*	*630*
3	United States*	323,526,036	Country with known data	0.90%	0.78%	1.03%	2,911,734	2,537,296	3,340,855

*country with original data; *locations with no data where estimates were imputed based on other locations within the regions are italicized*

** Population size ages 15-64 years from: Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 (GBD 2015) Population Estimates 1970-2015. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016.

CI = Confidence Interval

As can clearly be seen in Figure 5 below, there are very few places on the global map for which data is available, whether original or estimated. It is noted that only two locations – the US and Germany – have original POD data available (i.e. data not calculated from cross-walk) in the High Income Super-region (representing 34 countries / territories). The only other original POD data available is from Egypt in the North Africa and Middle East Super-region (which comprises 21 countries / territories). Super-regions with no data found through this systematic review include Southeast Asia, East Asia and Oceania (28 countries / territories); Central Europe, Eastern Europe and Central Asia (29 countries / territories); Latin America and Caribbean (32 countries / territories); South Asia (5 countries / territories); and Sub-Saharan Africa (46 countries / territories). This highlights the huge gap that currently exists within the database for PO NMU and dependence.

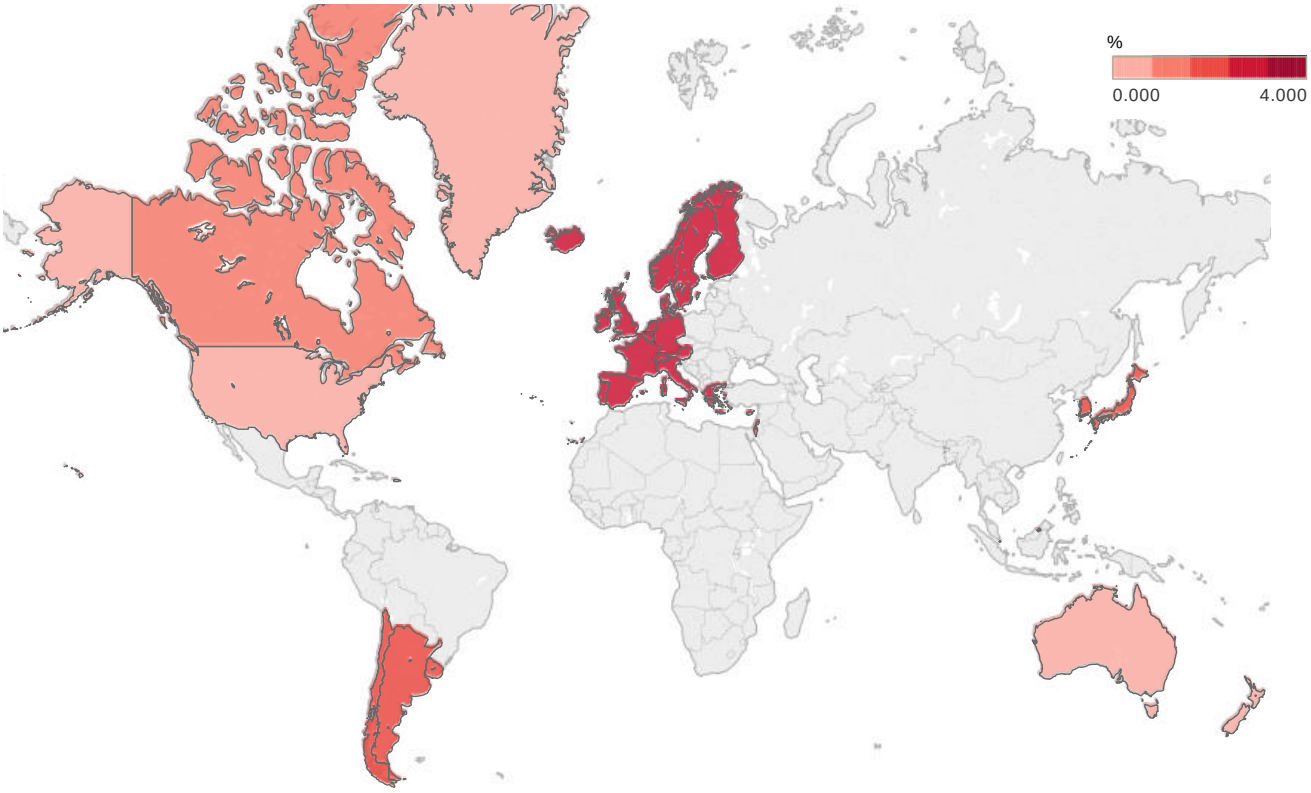

Figure 5: Map of High-Income Super-Region Estimated Prevalence of Prescription Opioid Dependence Using Cross-Walked Data

4. Discussion

The increasing trends of NMUPO prevalence has become a concern, and mapping the global prevalence of POD has become imperative to quantify the burden of disease due to POs, as well as to better inform prevention and treatment programs. This study systematically reviewed all recent peer-reviewed literature on the prevalence of NMUPO and POD.

The highest prevalence of POD prior to further adjustments and estimation of data is 3.4% in Germany. This is higher than the results of the GBD 2015 study (which focused on heroin) results (34), and showed prevalence estimates of 0.38% (0.34-0.43%). This highlights how easily important data can be missed if studies continue to examine prevalence data for heroin only, without taking into consideration PO data.

Cross-walk meta-analysis using data from studies with POD and NMUPO prevalence gave a pooled RR of 0.19. This ratio was used to adjust the prevalence of available NMUPO data towards the POD prevalence in the High Income Super-region, which had the most data available for analysis. It is thought that an estimated POD prevalence is more valuable than having no data for POD prevalence at all. After application of the cross-walk RR, results on weighted prevalence within the High Income Super-regions show that the region with the highest estimated POD prevalence was Western Europe (3.77%, 2.93-4.89%), while the region with the lowest estimate was Australasia (0.89%, 0.74-1.07%). This higher estimated prevalence was driven by the high NMUPO and POD prevalence data from Germany and Spain. This result is surprising, as it was expected that the region with the highest prevalence would be High Income North America, as the US lies within this region (see Figure 6). The overall super-regional estimate of prevalence of POD for the High Income Super-region was 2.43% (1.92 – 3.13%). The GBD 2015 results on the prevalence of opioid dependence in the High Income Super-region was 0.38% (0.34-0.43%), which potentially suggests that the burden of opioid dependence estimated without considering POs may be an underestimate.

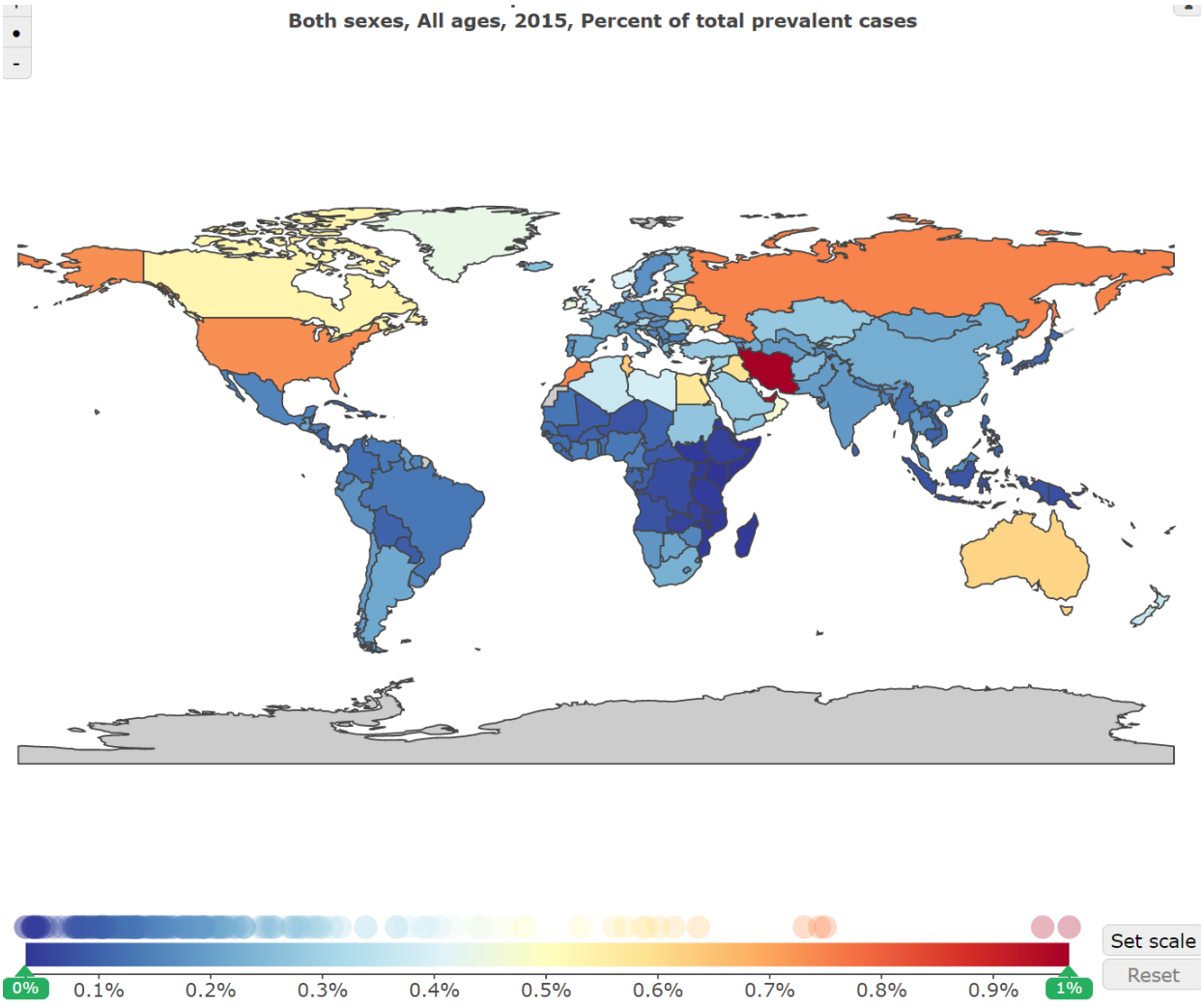

Figure 6 Prevalence of Opioid Use Disorders from the Global Burden of Disease 2015 Findings (figure from GBD Compare online) (35)

The GBD study looks at substance dependence globally, with a focus on cannabis, opioids, cocaine and amphetamines. However, the GBD study does not differentiate between prescription and illicit opioids, and therefore does not do a separate analysis on POD or NMUPOs. The current GBD 2015 study focuses predominantly on heroin (36), as this is traditionally where the highest disease burden lies. The GBD study also uses data that originates mainly in high-income countries, due to the availability and accessibility of data sources, with a minimal number of studies from other countries, as there has been a paucity of data from other parts of the world (37). The World Mental Health Survey (WMHS), undertaken by the World Health Organization (WHO), is considered the Gold Standard mental health resource globally (38). However, the WMHS only describes the overall prevalence of substance dependence and includes all the substances together. The WMHS does not examine opioids – illicit or prescription – as a separate entity.

Therefore, and as far as the author is aware, this is the first global systematic review and meta-analysis of NMUPO and POD conducted, and as such is an important contribution to the current body of literature. This study gives an overview of the available literature and data on prescription opioid nonmedical use and dependence globally, and highlights the significant gaps that currently exist within the literature.

4.1 United States Data

Most data-points are from the US (61 out of 114), and the overwhelming majority of data-points in the cross-walk to dependence are also from the US (44 out of 58) (Table 3 and Table 4). Despite not having the highest POD prevalence extrapolated within this project, POD and mortality have been increasing markedly in the US, even when compared to countries of a similar economic level (4). The US has a different demographic and social profile to other regions of the world, with regards to its affluence, political structure and health structure. A major difference is the ability of pharmaceutical companies to legally market their products directly to the general consumer (4), thereby creating a demand for a particular product as portrayed by advertising (regardless of its medical indication), drug interactions or risks. The prescription of POs has been shown to increase consumer satisfaction with physicians in the US (4).

In the past, physicians have been encouraged to prescribe opioid medication for pain, and this trend has continued in the US despite current misgivings regarding its efficacy in chronic, non-cancer pain (4, 39). Some physicians have even been known to prescribe POs without interviewing the patient, contributing to schemes known as “pill mills” (4). Even methadone, usually reserved for observed OST for opioid dependence in other countries, is increasingly prescribed as pain relief in the US, despite knowledge that side effects are greater and risk of overdose higher with methadone compared to other POs, such as oxycodone or tramadol (4). Another poor prescribing practice evidenced in the US is the concurrent prescription of opioids and benzodiazepines (BZDs), a sedative and anxiolytic class of medications. BZDs are thought to increase the dependent component of opioids through various neuro-mechanisms, and trends of both classes of medications are on the rise in the US (4).

One of the factors affecting the increasing trends of NMUPO in the US may be the reportedly high price of heroin in the US compared to POs (4); for example, $450/g in the US, and $62/g in the UK, as reported in the World Drug Report 2012 (in Weisberg et al, 2014). The relative price of, and access to, heroin and POs have been shown to affect the preference of the user, and these drugs have been shown to “share a market” (4). These drugs also share a high level of morbidity and mortality, and NMUPO should be as closely monitored as heroin use, as it can be just as unsafe taken illicitly.

4.2 Heroin Use

There were four studies accepted and only five data-points extracted on heroin use and dependence after the screening process. Most studies screened focused on heroin users or treatment groups, and were therefore excluded from this analysis. Heroin use prevalence among 16-18 year olds in Thailand was 1.52% (Wongtongkam et al 2015) (40), and 0.73% among 18-25 year olds in the US (Ihongbe and Masho, 2016) (6). Heroin dependence prevalence was 0.21% among 15-65 year olds in the Czech Republic (Sopko et al, 2016) (41). Data from the EMCDDA showed <0.01% prevalence of heroin dependence in both Italy and Spain. The low prevalence of heroin dependence in Spain is surprising given the high prevalence of NMUPO given in the Aguilar-Palacio et al (2014) (42) study (23.3%) and the resulting high, imputed POD prevalence estimate in Spain (4.39%).

In the US, heroin dependence among 18-25 year olds had a much lower prevalence compared to other opioids (like codeine) in a similar age group (0.73% compared to 9.6%). This is most likely due to reduced access to illicit drugs compared to over-the-counter opioids, as well as the perceived higher safety of over-the-counter opioids compared to heroin. However, these age demographics are not representative of the general population. There have been reports of problem heroin use in Asia (43), particularly in China, Pakistan, Iran and India (14), but results from this project found no data available on POD for these countries. Further data is required to examine if NMUPOs and POD is a concern in locations outside of high-income regions.

4.3 Age and Sex Demographics

School-based studies appear to have a higher prevalence of NMUPO, and this signifies that adolescents and young adults are more at risk of NMUPO. This could be due to an increased desire and willingness to experiment in this age group, or could be an indicator of increasing stress in today's younger population. However, this could also be partially attributed to unreliability of self-report in this age group. All school-based studies extracted for this project showed only NMUPOs and not POD (Fischer et al, 2013, Currie and Wild, 2012, Brands et al, 2010, McCabe et al, 2013, Catalano et al 2011, Biondo and Chilcoat, 2014), with one exception (Bassiony et al, 2015). The cross-walk ratio calculated for the adjustment of NMUPO prevalence to POD prevalence may not be applicable to a school-age sample, however, and further studies employing a cross-walk analysis to impute POD prevalence data should consider a separate cross-walk analysis for school-based data.

In the Egyptian study containing both NMUPO and POD prevalence data (Bassiony et al, 2015), 18 students out of 204 sampled in this study used POs non-medically, while one student was PO dependent (44). Dependence was identified using the Drug Use Disorders Identification Test (based on the Alcohol Use

Disorders Identification Test by the WHO). It is suggested that further studies examining NMUPO and POD use standardised assessment tools, as well as DSM or ICD criteria, to identify PO NMU and dependence in school-based samples. This provides a more reliable evidence base to identify those students most at risk, and to assist in the appropriate development of more intense and tailored interventions for this age demographic.

On the other end of the spectrum, and with the increase in opioid prescribing trends, the older age groups (who are more prone to chronic, painful medical conditions such as osteoarthritis or back pain) are also at risk of PO NMU and dependence. As this age group (50+ years) increases in numbers due to longer life expectancies in many countries, the amounts of POs prescribed to this demographic, and all the problems associated with this, will also increase. This is something clinicians must be aware of and take into consideration when prescribing pain treatments. It may be of benefit for physicians to be educated on other pain management methods, and for the health system to adequately compensate health practitioners when prescribing non-opioid treatments, to encourage more beneficial management plans, which may also be more time-consuming.

There were a total of four studies in this analysis that presented data stratified by sex on POD, and only two of those studies had valid data on both NMUPO and POD. Currently, the demographic with the highest burden due to opioid use disorder is young males (12), as this is the group with the highest prevalence of heroin dependence. However, this may change if POD continues to increase, and other age groups and female sex increase in prevalence. Due to the lack of data, analyses according to sex were not possible in this project. However, it would be useful to analyse results stratified by sex in future studies when more results become available, as results may differ significantly according to sex. This will contribute to our understanding of the disease burden due to POs, and help target prevention and intervention strategies.

4.4 Limitations

There were a number of limitations to this study, and it is advisable, therefore, to interpret and use these study results with due consideration. There were only four studies, and four data points used, to perform the cross-walk analysis to obtain the RR of 0.19 in this study. All studies in this cross-walk were from the US, and one study was from 2002. Given the above, this RR is US specific, but as it uses all the data available from this project, this is the RR used to impute estimated prevalences for POD in all countries with available NMUPO data and no POD data.

Estimated weighted prevalences of POD were imputed for the High Income Super-region, leaving much of the world unaccounted for. Even in this super-region however, the overwhelming majority of the data (29 countries out of 34) were imputed. Only five countries had data from original studies available for use, as

identified in this project, and not all of the data had age ranges representative of the general population, with some studies having younger age ranges (eg. Brands et al, 2010: age 12-19 years old).

As well as this, and even though of some benefit compared to no data, it must be remembered that most of the POD prevalence estimates in this paper are extrapolated from NMU data, and actual POD prevalence may be higher or lower. However, a standardized method to make adjustments was used, and standard errors from original data and the cross-walk ratios were incorporated into the adjustments, which form a standardized basis for PO prevalence estimates based on the current available data. Future studies that collect data on POD can help assess the validity of these findings, and provide better data to inform the cross-walk ratio and further adjustments.

During the development of the study design, it was planned to analyse the data according to sex, to enable a comparison of males to females globally. This was not possible, however, as there was a paucity of data available (only two studies) with both NMUPO and POD that stratified data according to sex. It was also planned to map POD for all super-regions and regions globally, but this was also not possible due to the lack of data.

There may be data for other regions and super-regions available in other languages in local journals (e.g. Spanish and Portuguese articles for the Latin America and Caribbean Super-region), or within the grey literature, but, although we did not exclude non-English articles, due to English search strings, these studies may not have been picked up in this systematic review. This paucity of data on POs has previously been documented by other studies, however. A systematic review by Degenhardt et al (2011) revealed studies from 25 countries pertaining to opioid dependence. All studies, however, focused on heroin or illicit opioids (45).

4.5 Future Areas of Research

The paucity of data globally has been highlighted in this paper, particularly in regions that are less economically affluent. General population surveys – local or national – can be costly, time-consuming and resource intensive, and it may be understandable that authorities use precious resources elsewhere. Therefore, an alternative approach to population-based surveys suggested is analysis of wastewater. This method is gaining recognition internationally, and is quick, cost-effective and not as human resource intensive (46-50). Wastewater analysis uses the measurement of target drug excretion residues, or metabolites, found in sewage wastewater (47), and has been shown to give similar, comparative results to population surveys (51). It gives a timely snapshot of relevant metabolites and can elicit daily, weekly, fortnightly etc changes in opioid use (49). The disadvantage of this method is that, while it can provide data on the overall amount of drugs used by the community, this method does not provide data on the number

of users. In addition, PO and illicit opioids cannot yet be distinguished, as the target metabolites measured are the same. However, there are slightly different pathways of metabolism, and if this area of research is seriously considered, it may be possible to find different, measurable target metabolites to differentiate between illicit and POs. While not as effective as population-based surveys, wastewater analysis has the potential to analyse the overall amounts and types of drugs used within the community, particularly in lower resourced areas.

4.6 Conclusion

This study has found prevalence of POD up to 3.4% in some countries, with the highest estimated POD prevalence data in the Western European region. This result was unexpected, and highlights the need for further research to elicit the actual prevalence and burden of POD globally. The increasing trends of NMUPO and POD prevalence are of increasing concern. However, the prevalence of POD is not able to be mapped globally given the current lack of data in many regions of the world. Some evidence exists that POD poses a large burden on the community, even overtaking the burden of heroin use in some places, but this is not yet able to be validated. A quantification of the epidemiology and disease burden of POs enables the timely and efficacious implementation of cost-effective prevention and intervention strategies, and this may be able to save much morbidity and mortality globally.

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6. APPENDICES

6.1 Appendix 6.1: Database Search Strategy and Strings

Search Terms for Global Burden of Disease 2016
Epidemiology of opioids, cocaine, amphetamine, and cannabis use or dependence

Search strategy
Search ((1 & 2) OR 3) & 4

Group 1: substance (everything within this group OR)

adderall (within title and abstract)
Amphetamin* (within title and abstract)
analges* (within title and abstract)
Cannabis (within title and abstract)
Cocaine (within title and abstract)
codeine (within title and abstract)
Crack (within title and abstract)
Hashish (within title and abstract)
heroin (within title and abstract)
“illicit drug” (within title and abstract)
“illicit substance” (within title and abstract)
Marijuana (within title and abstract)
Methamphetam* (within title and abstract)
narcotic* (within title and abstract)
opiate* (within title and abstract)
opioid* (within title and abstract)
oxycodone (within title and abstract)
oxycotin (within title and abstract)
pain-reli* (within title and abstract)
“pain relief” (within title and abstract)
“pain reliever” (within title and abstract)
“prescription drug” (within title and abstract)
“prescription substance” (within title and abstract)
ritalin (within title and abstract)

Shabu (within title and abstract)
Stimulant* (within title and abstract)
Substance (within title and abstract)
vicodin (within title and abstract)
Yaba (within title and abstract)

Group 2: use or dependence (everything within this group OR)
abus* (within title and abstract)
addict* (within title and abstract)
consum* (within title and abstract)
dependen* (within title and abstract)
misus* (within title and abstract)
non-medic* (within title and abstract)
smok* (within title and abstract)
use (within title and abstract)

Dependency (psychology) (MeSH term)

Group 3: substance use or substance dependence Mesh terms (everything within this group OR)

“cannabis addiction” (Emtree term)
“cannabis smoking” (Emtree term)
“cannabis use” (Emtree term)
“cocaine dependence” (Emtree term)
“Drug abuse pattern” (Emtree term)
“Drug abuse” (Emtree term)
“Drug dependence” (Emtree term)
“Drug misuse” (Emtree term)
“Drug use” (Emtree term)
“heroin dependence” (Emtree term)
“methamphetamine dependence” (Emtree term)
“narcotic dependence” (Emtree term)
“Substance abuse” (Emtree term)

“Drug users” (MeSH term)
“Heroin dependence” (MeSH term)
“Marijuana abuse” (MeSH term)

“Marijuana smoking” (MeSH term)
“Morphine dependence” (MeSH term)
“Prescription drug diversion” (MeSH term)
“Prescription drug misuse” (MeSH term)
“Prescription drug overuse” (MeSH term)
“Substance-related disorders” (MeSH term)

“Drug abuse” (PsycINFO term)
“Drug addiction” (PsycINFO term)
“Drug dependence” (PsycINFO term)
“Drug dependency” (PsycINFO term)
“Drug usage” (PsycINFO term)
“Heroin addiction” (PsycINFO term)
“Marijuana usage” (PsycINFO term)
“Substance abuse and addiction measures” (PsycINFO term)
“Substance use disorder” (PsycINFO term)

Group 4: Parameter-specific search terms (everything within this group OR)
death* (within title and abstract)
duration (within title and abstract)
epidemiolog* (within title and abstract)
inciden* (within title and abstract)
mortality* (within title and abstract)
prevalen* (within title and abstract)
recurren* (within title and abstract)
remission (within title and abstract)
remit* (within title and abstract)

Cohort studies (MeSH term)
Cross-sectional studies (MeSH term)
Epidemiology (Mesh term)
Incidence (Mesh term)
Mortality (Mesh term)
Prevalence (Mesh term)
Recurrence (Mesh term)

Incidence (Emtree term)

Morbidity (Emtree term)
Mortality rate (Emtree term)
Prevalence (Emtree term)
Recurrence risk (Emtree term)
Recurrent disease (Emtree term)
Remission (Emtree term)

Mortality rate (PsycINFO term)
Relapse (Disorders) (PsycINFO term)
Remission (Disorders) (PsycINFO term)

Psycinfo search via EBSCOhost, conducted date 2016.09.16

(((TI adderall OR AB adderall OR TI Amphetamin* OR AB Amphetamin* OR TI analges* OR AB analges* OR TI Cannabis OR AB Cannabis OR TI Cocaine OR AB Cocaine OR TI codeine OR AB codeine OR TI Crack OR AB Crack OR TI Hashish OR AB Hashish OR TI heroin OR AB heroin OR TI “illicit drug” OR AB “illicit drug” OR TI “illicit substance” OR AB “illicit substance” OR TI Marijuana OR AB Marijuana OR TI Methamphetam* OR AB Methamphetam* OR TI narcotic* OR AB narcotic* OR TI opiate* OR AB opiate* OR TI opioid* OR AB opioid* OR TI oxycodone OR AB oxycodone OR TI oxycotin OR AB oxycotin OR TI pain-reli* OR AB pain-reli* OR TI “pain relief” OR AB “pain relief” OR TI “pain reliever” OR AB “pain reliever” OR TI “prescription drug” OR AB “prescription drug” OR TI “prescription substance” OR AB “prescription substance” OR TI ritalin OR AB ritalin OR TI Shabu OR AB Shabu OR TI Stimulant* OR AB Stimulant* OR TI Substance OR AB Substance OR TI vicodin OR AB vicodin OR TI Yaba OR AB Yaba) AND (TI abus* OR AB abus* OR TI addict* OR AB addict* OR TI consum* OR AB consum* OR TI dependen* OR AB dependen* OR TI misus* OR AB misus* OR TI non-medic* OR AB non-medic* OR TI smok* OR AB smok* OR TI use OR AB use OR MA Dependency)) OR (MA “Drug users” OR MA “Heroin dependence” OR MA “Marijuana abuse” OR MA “Marijuana smoking” OR MA “Morphine dependence” OR MA “Prescription drug diversion” OR MA “Prescription drug misuse” OR MA “Prescription drug overuse” OR MA “Substance-related disorders” OR KW “Drug abuse” OR KW “Drug addiction” OR KW “Drug dependence” OR KW “Drug dependency” OR KW “Drug usage” OR KW “Heroin addiction” OR KW “Marijuana usage” OR KW “Substance abuse and addiction measures” OR KW “Substance use disorder)) AND (TI prevalen* OR AB prevalen* OR TI mortality* OR AB mortality* OR TI death* OR AB death* OR TI inciden* OR AB inciden* OR TI recurren* OR AB recurren* OR TI remission OR AB remission OR TI duration OR AB duration OR TI remit* OR AB remit* OR TI epidemiolog* OR AB epidemiolog* OR KW Mortality rate OR KW Relapse OR KW Remission OR MA Cohort studies OR MA Cross-sectional studies OR MA Epidemiology OR MA Incidence OR MA Mortality OR MA Prevalence OR MA Recurrence)

Limiters - Publication Year: 2009-; Publication Type: Peer Reviewed Journal; Population Group: Human
Search modes - Boolean/Phrase

Result
12180

Medline search via EBSCOhost, conducted date 2016.09.16

(((TI adderall OR AB adderall OR TI Amphetamin* OR AB Amphetamin* OR TI analges* OR AB analges* OR TI Cannabis OR AB Cannabis OR TI Cocaine OR AB Cocaine OR TI codeine OR AB codeine OR TI Crack OR AB Crack OR TI Hashish OR AB Hashish OR TI heroin OR AB heroin OR TI “illicit drug” OR AB “illicit drug” OR TI “illicit substance” OR AB “illicit substance” OR TI Marijuana OR AB Marijuana OR TI Methamphetam* OR AB Methamphetam* OR TI narcotic* OR AB narcotic* OR TI opiate* OR AB opiate* OR TI opioid* OR AB opioid* OR TI oxycodone OR AB oxycodone OR TI oxycotin OR AB oxycotin OR TI pain-reli* OR AB pain-reli* OR TI “pain relief” OR AB “pain relief” OR TI “pain reliever” OR AB “pain reliever” OR TI “prescription drug” OR AB “prescription drug” OR TI “prescription substance” OR AB “prescription substance” OR TI ritalin OR AB ritalin OR TI Shabu OR AB Shabu OR TI Stimulant* OR AB Stimulant* OR TI Substance OR AB Substance OR TI vicodin OR AB vicodin OR TI Yaba OR AB Yaba) AND (TI abus* OR AB abus* OR TI addict* OR AB addict* OR TI consum* OR AB consum* OR TI dependen* OR AB dependen* OR TI misus* OR AB misus* OR TI non-medic* OR AB non-medic* OR TI smok* OR AB smok* OR TI use OR AB use OR MM Dependency OR MH Dependency)) OR (MH “Drug users” OR MH “Heroin dependence” OR MH “Marijuana abuse” OR MH “Marijuana smoking” OR MH “Morphine dependence” OR MH “Prescription drug diversion” OR MH “Prescription drug misuse” OR MH “Prescription drug overuse” OR MH “Substance-related disorders” OR MM “Drug users” OR MM “Heroin dependence” OR MM “Marijuana abuse” OR MM “Marijuana smoking” OR MM “Morphine dependence” OR MM “Prescription drug diversion” OR MM “Prescription drug misuse” OR MM “Prescription drug overuse” OR MM “Substance-related disorders” OR KW “Drug abuse” OR KW “Drug addiction” OR KW “Drug dependence” OR KW “Drug dependency” OR KW “Drug usage” OR KW “Heroin addiction” OR KW “Marijuana usage” OR KW “Substance abuse and addiction measures” OR KW “Substance use disorder)) AND (TI prevalen* OR AB prevalen* OR TI mortality* OR AB mortality* OR TI death* OR AB death* OR TI inciden* OR AB inciden* OR TI recurren* OR AB recurren* OR TI remission OR AB remission OR TI duration OR AB duration OR TI remit* OR AB remit* OR TI epidemiolog* OR AB epidemiolog* OR KW Mortality rate OR KW Relapse OR KW Remission OR MH Cohort studies OR MH Cross-sectional studies OR MH Epidemiology OR MH Incidence OR MH Mortality OR MH Prevalence OR MH Recurrence OR MM Cohort studies OR MM Cross-sectional studies OR MM Epidemiology OR MM Incidence OR MM Mortality OR MM Prevalence OR MM Recurrence)

Limiters - Date of Publication: 20090101-; Human; Journal & Citation Subset: MEDLINE, Pubmed Central; Publication Type: Journal Article
Search modes - Boolean/Phrase

Results
18930

Embase search, conducted date 2016.09.16

adderall:ab,ti OR amphetamin*:ab,ti OR analges*:ab,ti OR cannabis:ab,ti OR cocaine:ab,ti OR codeine:ab,ti OR crack:ab,ti OR hashish:ab,ti OR heroin:ab,ti OR 'illicit drug':ab,ti OR 'illicit substance':ab,ti OR marijuana:ab,ti OR methamphetam*:ab,ti OR narcotic*:ab,ti OR opiate*:ab,ti OR opioid*:ab,ti OR oxycodone:ab,ti OR oxycotin:ab,ti OR 'pain reli*':ab,ti OR 'pain relief':ab,ti OR 'pain reliever':ab,ti OR 'prescription drug':ab,ti OR 'prescription substance':ab,ti OR ritalin:ab,ti OR shabu:ab,ti OR stimulant*:ab,ti OR substance:ab,ti OR vicodin:ab,ti OR yaba:ab,ti AND (abus*:ab,ti OR addict*:ab,ti OR consum*:ab,ti OR dependen*:ab,ti OR misus*:ab,ti OR 'non medic*':ab,ti OR smok*:ab,ti OR use:ab,ti) OR 'cannabis addiction'/exp OR 'cannabis smoking'/exp OR 'cannabis use'/exp OR 'cocaine dependence'/exp OR 'drug abuse pattern'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'drug misuse'/exp OR 'drug use'/exp OR 'heroin dependence'/exp OR 'methamphetamine dependence'/exp OR 'narcotic dependence'/exp OR 'substance abuse'/exp AND (death*:ab,ti OR duration:ab,ti OR epidemiolog*:ab,ti OR inciden*:ab,ti OR mortality:ab,ti OR prevalen*:ab,ti OR recurren*:ab,ti OR remission:ab,ti OR remit:ti OR incidence:ab,ti OR morbidity:ab,ti OR 'mortality rate'/exp OR 'prevalence'/exp OR 'recurrence risk'/exp OR 'recurrent disease'/exp OR 'remission'/exp) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [embase]/lim AND [2009-2016]/py

Results
30266

6.2 Appendix 6.2: World Regions

Table 6: Location Level and Identification of Super-Regions (1), Regions (2) and Countries/Territories (3)

LEVEL	LOCATION NAME
1	SOUTHEAST ASIA, EAST ASIA, AND OCEANIA
2	East Asia
3	China
3	North Korea
3	Taiwan
2	Southeast Asia
3	Cambodia
3	Indonesia
3	Laos
3	Malaysia
3	Maldives
3	Mauritius
3	Myanmar
3	Philippines
3	Sri Lanka
3	Seychelles
3	Thailand
3	Timor-Leste
3	Vietnam
2	Oceania
3	American Samoa
3	Federated States of Micronesia
3	Fiji
3	Guam
3	Kiribati
3	Marshall Islands
3	Northern Mariana Islands
3	Papua New Guinea
3	Samoa
3	Solomon Islands
3	Tonga

3	Vanuatu
1	CENTRAL EUROPE, EASTERN EUROPE, AND CENTRAL ASIA
2	Central Asia
3	Armenia
3	Azerbaijan
3	Georgia
3	Kazakhstan
3	Kyrgyzstan
3	Mongolia
3	Tajikistan
3	Turkmenistan
3	Uzbekistan
2	Central Europe
3	Albania
3	Bosnia and Herzegovina
3	Bulgaria
3	Croatia
3	Czech Republic
3	Hungary
3	Macedonia
3	Montenegro
3	Poland
3	Romania
3	Serbia
3	Slovakia
3	Slovenia
2	Eastern Europe
3	Belarus
3	Estonia
3	Latvia
3	Lithuania
3	Moldova
3	Russia
3	Ukraine
1	HIGH-INCOME
2	High-income Asia Pacific
3	Brunei

3	Japan
3	South Korea
3	Singapore
2	Australasia
3	Australia
3	New Zealand
2	Western Europe
3	Andorra
3	Austria
3	Belgium
3	Cyprus
3	Denmark
3	Finland
3	France
3	Germany
3	Greece
3	Ireland
3	Israel
3	Italy
3	Luxembourg
3	Malta
3	Netherlands
3	Norway
3	Portugal
3	Spain
3	Sweden
3	Switzerland
3	United Kingdom
2	Southern Latin America
3	Argentina
3	Chile
3	Uruguay
2	High-income North America
3	Canada
3	Greenland
3	United States
1	LATIN AMERICA AND CARIBBEAN

2	Caribbean
3	Antigua and Barbuda
3	The Bahamas
3	Barbados
3	Belize
3	Bermuda
3	Cuba
3	Dominica
3	Dominican Republic
3	Grenada
3	Guyana
3	Haiti
3	Jamaica
3	Puerto Rico
3	Saint Lucia
3	Saint Vincent and the Grenadines
3	Suriname
3	Trinidad and Tobago
3	Virgin Islands, U.S.
2	Andean Latin America
3	Bolivia
3	Ecuador
3	Peru
2	Central Latin America
3	Colombia
3	Costa Rica
3	El Salvador
3	Guatemala
3	Honduras
3	Mexico
3	Nicaragua
3	Panama
3	Venezuela
2	Tropical Latin America
3	Brazil
3	Paraguay
1	NORTH AFRICA AND MIDDLE EAST

2	North Africa and Middle East
3	Afghanistan
3	Algeria
3	Bahrain
3	Egypt
3	Iran
3	Iraq
3	Jordan
3	Kuwait
3	Lebanon
3	Libya
3	Morocco
3	Palestine
3	Oman
3	Qatar
3	Saudi Arabia
3	Sudan
3	Syria
3	Tunisia
3	Turkey
3	United Arab Emirates
3	Yemen
1	SOUTH ASIA
2	South Asia
3	Bangladesh
3	Bhutan
3	India
3	Nepal
3	Pakistan
1	SUB-SAHARAN AFRICA
2	Central Sub-Saharan Africa
3	Angola
3	Central African Republic
3	Congo
3	Democratic Republic of the Congo
3	Equatorial Guinea
3	Gabon

2	Eastern Sub-Saharan Africa
3	Burundi
3	Comoros
3	Djibouti
3	Eritrea
3	Ethiopia
3	Kenya
3	Madagascar
3	Malawi
3	Mozambique
3	Rwanda
3	Somalia
3	South Sudan
3	Tanzania
3	Uganda
3	Zambia
2	Southern Sub-Saharan Africa
3	Botswana
3	Lesotho
3	Namibia
3	South Africa
3	Swaziland
3	Zimbabwe
2	Western Sub-Saharan Africa
3	Benin
3	Burkina Faso
3	Cameroon
3	Cape Verde
3	Chad
3	Cote d'Ivoire
3	The Gambia
3	Ghana
3	Guinea
3	Guinea-Bissau
3	Liberia
3	Mali
3	Mauritania

3	Niger
3	Nigeria
3	Sao Tome and Principe
3	Senegal
3	Sierra Leone
3	Togo

1 = Super-region

2 = Region

3 = Country / Territory

6.3 Appendix 6.3: List of Studies in Table 3

1. Aguilar-Palacio I, Carrera-Lasfuentes P, Poblador-Plou B, Prados-Torres A, Rabanaque-Hernández MJ. [Morbidity and drug consumption. Comparison of results between the National Health Survey and electronic medical records]. Gaceta Sanitaria / SESPAS. 2014;28(1):41-7.
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12. Fischer B, Ialomiteanu A, Boak A, Adlaf E, Rehm J, Mann RE. Prevalence and key covariates of non-medical prescription opioid use among the general secondary student and adult populations in Ontario, Canada. Drug And Alcohol Review. 2013;32(3):276-87.

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6.4 Appendix 6.4: Statistical Data Results for Cross-walk Meta-Analyses

Table 7: Meta-Analysis Including All Studies with Prescription Opioid Nonmedical Use and Dependence Data

Study Details				
	RR	LCI 95%	HCI 95%	Weight (%)
Back (2010), United States, age 12-99, year 2006	0.1327	0.1217	0.1447	7.4528
Bassiony (2015), Egypt, age 12-99, year 2013	0.0556	0.0075	0.4123	0.2617
Han (2015), United States, age 18-99, year 2003	0.1111	0.0977	0.1263	7.0217
Han (2015), United States, age 18-99, year 2004	0.1176	0.1035	0.1337	7.0242
Han (2015), United States, age 18-99, year 2005	0.1296	0.1151	0.1460	7.1294
Han (2015), United States, age 18-99, year 2006	0.1207	0.1070	0.1361	7.1161
Han (2015), United States, age 18-99, year 2007	0.1404	0.1254	0.1571	7.2000
Han (2015), United States, age 18-99, year 2008	0.1509	0.1349	0.1689	7.2014
Han (2015), United States, age 18-99, year 2009	0.1607	0.1445	0.1788	7.2626
Han (2015), United States, age 18-99, year 2010	0.1636	0.1471	0.1820	7.2650
Han (2015), United States, age 18-99, year 2011	0.1633	0.1459	0.1827	7.2004
Han (2015), United States, age 18-99, year 2012	0.1786	0.1613	0.1977	7.3099
Han (2015), United States, age 18-99, year 2013	0.1837	0.1648	0.2047	7.2436
Martins (2010), United States, age 18-57, year 2001-02	0.2559	0.2107	0.3109	6.1687
Saha (2016), United States, age 18-99, year 2012-13	0.2090	0.1858	0.2351	7.1424
Pooled	0.15	0.14	0.17	100
Statistics				
I-squared	90.8532	86.6097	93.7518	
Cochrane's Q	153.0582			
Chi2, p	0			
tau2	0.0360			

Table 8: Meta-Analysis Without Egyptian (Bassiony 2015) Study Data

Study	RR	LCI 95%	HCI 95%	Weight (%)
Back (2010), United States, age 12-99, year 2006	0.1327	0.1217	0.1447	7.4722
Han (2015), United States, age 18-99, year 2003	0.1111	0.0977	0.1263	7.0401
Han (2015), United States, age 18-99, year 2004	0.1176	0.1035	0.1337	7.0427
Han (2015), United States, age 18-99, year 2005	0.1296	0.1151	0.1460	7.1481
Han (2015), United States, age 18-99, year 2006	0.1207	0.1070	0.1361	7.1347
Han (2015), United States, age 18-99, year 2007	0.1404	0.1254	0.1571	7.2189
Han (2015), United States, age 18-99, year 2008	0.1509	0.1349	0.1689	7.2203
Han (2015), United States, age 18-99, year 2009	0.1607	0.1445	0.1788	7.2816
Han (2015), United States, age 18-99, year 2010	0.1636	0.1471	0.1820	7.2840
Han (2015), United States, age 18-99, year 2011	0.1633	0.1459	0.1827	7.2193
Han (2015), United States, age 18-99, year 2012	0.1786	0.1613	0.1977	7.3290
Han (2015), United States, age 18-99, year 2013	0.1837	0.1648	0.2047	7.2626
Martins (2010), United States, age 18-57, year 2001-02	0.2559	0.2107	0.3109	6.1853
Saha (2016), United States, age 18-99, year 2012-13	0.2090	0.1858	0.2351	7.1612
Pooled	0.15	0.14	0.17	100
Statistics				
I-squared	91.4525	87.4073	94.1983	
Cochrane's Q	152.0920			
Chi2, p	0			
tau2	0.0360			

Table 9: Meta-Analysis Without Egyptian (Bassiony 2015) Study Data and Only Most Recent Data from Han (2015) Study

Study				
	RR	LCI 95%	HCI 95%	Weight (%)
Back (2010), United States, age 12-99, year 2006	0.1327	0.1217	0.1447	25.8808
Han (2015), United States, age 18-99, year 2013	0.1837	0.1648	0.2047	25.4932
Martins (2010), United States, age 18-57, year 2001-02	0.2559	0.2107	0.3109	23.3242
Saha (2016), United States, age 18-99, year 2012-13	0.2090	0.1858	0.2351	25.3018
Pooled	0.19	0.14	0.25	100
Statistics				
I-squared	95.1707	90.5944	97.5204	
Cochrane's Q	62.1205			
Chi2, p	<0.001			
tau2	0.0702			

RR = risk ratio, LCI = lower confidence interval, HCI = higher confidence interval

6.5 Appendix 6.5: PRISMA Checklist

Section/topic	#	Checklist item	Reported from page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	8
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	9-
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	12
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	12-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	12
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	14
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	14

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	14
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	15
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	15
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	14
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	47
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	47