LIVERPOOL JOHN MOORES UNIVERSITY

CMO Alcohol Guidelines Review

Mapping systematic review level evidence

A report for the Health Evidence Expert Working Group
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About this document

This document was prepared on behalf of the Secretariat to the Health Evidence Expert Group by the Centre for Public Health, Liverpool John Moore University. The Health Evidence Expert Group was established by the UK Chief Medical Officers to review the evidence on the health impacts from alcohol.

The purpose of this document is to provide a map of the systematic review level evidence and to describe the type and quantity of published material on the health impacts from alcohol.

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1 Methods

1.1 Search strategy

A database of systematic reviews and meta-analyses was compiled from systematic searches of electronic sources (Medline, EMBASE and PsycINFO; see Appendix 1 for a sample search strategy), and selected, published reviews (Rehm et al., 2010) and recent reports on the development of alcohol guidelines in Canada (Butt et al., 2010) and Australia (National Health and Medical Research Council, 2009).

1.2 Inclusion and exclusion criteria

Systematic reviews and meta-analyses published since 1995 that synthesized data from studies on health and social impacts of alcohol exposure (any measure) were eligible for inclusion. One reviewer independently screened all titles and abstracts to identify any potentially relevant articles. Full titles of any titles/abstracts that were considered relevant were obtained for further screening and the relevance of each article reassessed against criteria to determine if the review was relevant to the research questions. These criteria were adapted from *Methods for the development of NICE public health guidance [third edition]* and were as follows:

1. Does the review address an appropriate and clearly-focused question that is relevant to one or more of the key review questions?

   Reviews that provided a clear description of the population(s) considered, comparators, and how the outcomes evaluated were selected for inclusion. Outcomes considered needed to be clearly described within the methodology, include a precise definition and how validated.

2. Does the review include the types of studies relevant to the key review questions?

   Only reviews that reported the types of studies sought (including any inclusion/exclusion criteria) were included. The inclusion of cohort and/or case-control studies was considered as the minimum design requirement for inclusion.

3. Is the literature search sufficiently rigorous to identify all the relevant studies?

   To be eligible, the methods used to locate studies needed to be clearly reported. As a minimum, reviews were required to have conducted searches of at least two databases and searched the reference lists of retrieved studies for further references.

4. Is the study quality of included studies appropriately assessed and reported?

Review needed to have used appropriate and clear criteria to assess the quality of the individual studies before deciding whether to include or exclude them. Reviews that did not include such an assessment were excluded.

5. Is an adequate description of the analytical methodology used included, and are the methods used appropriate to the question?

   The approach and meta-analytic techniques used to analyse the data needed to be clearly described and justified where appropriate. Approaches to dealing with heterogeneity including the specification of any subgroup analyses and sensitivity analyses needed to be reported for studies described as meta-analyses.

The criteria were used to identify systematic reviews and meta-analyses incorporating systematic methods of study retrieval and inclusion.

1.3 Data extraction

Data relating to the individual studies was extracted by one reviewer into a pre-designed form and then tabulated. Data extraction and tabulation included the following information (where available): author(s), year, aims; review search parameters; inclusion and exclusion criteria (including study design, date range and country); type of alcohol exposure (including whether specific beverage types were considered; dose and patterns of alcohol consumption); outcomes and methods of analysis (mortality and/or morbidity; threshold effects; sick quitter effect considered where appropriate); results (whether quantitative effect sizes calculated and confidence intervals).

1.4 Quality assessment

Quality assessment was undertaken using the AMSTAR measurement tool (see Appendix 2 for AMSTAR criteria). The tool consists of 11 items and has good face and content validity for measuring the methodological quality of systematic reviews. To derive a summary quality score for each study based on the AMSTAR tool, a score of 1 was awarded for each of the criteria marked with a ‘yes’ on the tool (or 0.5 for partially meeting the criteria). These scores were summed across the criteria to provide a score for each study out of a maximum possible score of 11.

2 Results of the mapping

2.1 Summary of study identification

A total of 2,068 references were identified through searches, of which 147 were identified as potentially relevant. Fifteen additional references were identified through reference screening.

Forty three references were excluded prior to full screening as they were not systematic reviews or meta-analyses (n=24); the population focus was not applicable to the UK (n=15); the topic was not applicable (n=4); they were foreign language articles (n=3) or a full text copy was not available (n=1). A further 16 articles were not screened against the full criteria as they were meta-analyses based on pooled analysis of data (n=10) or used a Mendelian randomisation approach (n=3).

A total of 103 articles were screened against the full criteria. The identified systematic reviews and meta-analyses examined the relationship between alcohol consumption and risk across the following diseases and health problems:

- Infectious and parasitic diseases (n=5)
- Neoplasms (n=37)
- Endocrine, nutritional and metabolic diseases (n=4)
- Mental and behavioural disorders (n=4)
- Diseases of the nervous system (n=1)
- Diseases of the eye (n=1)
- Diseases of the circulatory system (n=21)
- Diseases of the respiratory system (n=1)
- Diseases of the digestive system (n=3)
- Diseases of the skin and subcutaneous tissue (n=1)
- Diseases of the musculoskeletal system (n=2)
- Diseases of the genitourinary system (n=1)
- Pregnancy and conditions originating in the perinatal period (n=9)
- External causes of morbidity and mortality (n=6)

A further seven articles examined: all-cause mortality (n=2); multiple conditions (n=2); the adult consequences of alcohol consumption in adolescence (n=1); effects of alcohol use in older people (n=1); and the derivation of tolerable upper alcohol intake levels (n=1).

2.2 Outcomes of inclusion criteria screening

The outcomes of the inclusion criteria screening are presented in full in Table 11 in Appendix 4. Nineteen studies met all five criteria and a further 35 studies met four of the five criteria. Of the studies meeting four criteria: (i) 27 did not formally assess the quality of the included studies; (ii) four had not conducted a sufficiently rigorous literature search; (iii) three did not

provide an adequate description of the analytical methods used; and (iv) one included types of study designs not relevant to the review question (i.e. cross-sectional studies). Thirty eight studies met three criteria, with the majority of these studies (n=31) lacking a sufficiently rigorous search and formal quality assessment of the included studies. Due to the relatively low number of articles meeting all five inclusion criteria, the 92 articles which met three or more of the criteria were therefore considered for inclusion. The remaining 11 articles, which met two or fewer of the criteria, were poor quality or had not used relevant methodology (i.e. one article was a review of reviews) and were excluded from the review.

The 92 articles were organised according the broad disease/health problem area examined and then by the specific condition examined. For specific conditions where only one systematic review or meta-analysis was identified, the article was included. Where more than one systematic or meta-analyses examined a specific condition, the article meeting the highest number of criteria was included, or where it was not possible to select on the number of criteria, the most recently published article was selected. For a few conditions, it was not possible to select on the number of criteria or year (i.e. bladder cancer, renal cell cancer and atrial fibrillation) and two articles were included per condition in these cases. In total, 51 articles were selected for data extraction and quality assessment.

2.3 Outcomes of data extraction

A summary of the methods of the included systematic reviews and meta-analyses are presented in Table 12 in Appendix 5.

2.4 Outcomes of quality assessment

Scores on the AMSTAR tool ranged from 2 to 7.5; however the majority of reviews received a score of 5 or less (n=38; Figure 1). A summary of the AMSTAR tool measurement results for each study is presented in Table 15 in Appendix 5.

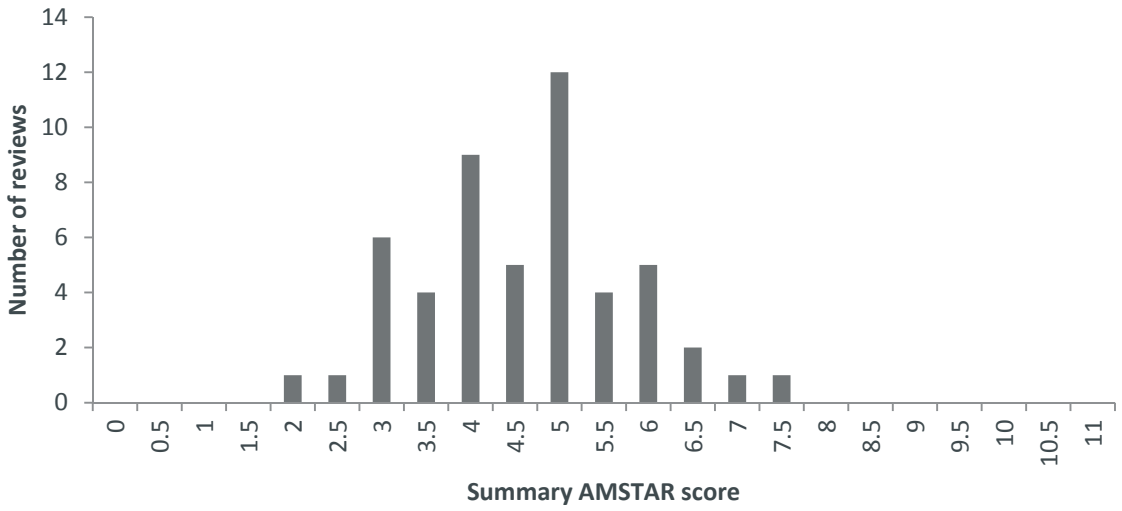

Figure 1. Summary of scores on the AMSTAR tool

None of the included systematic reviews and meta-analyses reported that an ‘a priori’ design had been used in the conduct of the review or meta-analysis. For 25 studies it was not possible to tell from the publication whether duplicate study selection and/or data extraction had been undertaken; for 5 studies it was clear that it had not been undertaken. In 11 reviews it was reported that duplicate study selection and data extraction had been undertaken. In a further 10 reviews either duplicate study selection or data extraction was reported to have been undertaken. The majority of reviews were based on a comprehensive literature search; 18 reviews were based on inadequate searches and two reviews were based on searches of at least two electronic sources but were not supplemented by other strategies. Authors of only a very small number of reviews reported that they searched for reports regardless of their publication type; the vast majority of reviews were limited to inclusion of English language and/or peer-reviewed publications. A list of studies included and excluded from the review were not commonly included in the publications. Whilst the majority of articles provided a flowchart for the inclusion and exclusion process, full reference details were generally not provided in the articles or in supplementary material. The characteristics of the included studies were provided in an aggregated form in most of the reviews; however a summary of data from the original studies was missing in seven reviews. The scientific quality of the included studies was assessed in 14 reviews and of these, only nine were judged to have used the scientific quality of the included studies appropriately in formulating conclusions. The methods used to combine the findings of studies were judged to be appropriate in all of the included studies. Four reviews did not undertake a meta-analysis and were based on a narrative synthesis. For the 47 systematic reviews that included a meta-analysis, all reported that heterogeneity tests were used to assess whether studies were combinable and the likelihood of publication bias was assessed in the majority of reviews.

Table 1. Summary of outcomes on the AMSTAR tool criteria

Criteria met?	AMSTAR measurement tool criteria										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Yes	0	11	31	3	4	44	13	9	50	25	34
Partially	0	10	2	0	6	0	1	0	0	13	0
No	0	5	18	33	40	7	37	4	0	9	17
Can't answer	51	25	0	15	1	0	0	1	1	0	0
Not applicable	0	0	0	0	0	0	0	37	0	4	0

2.5 Assessment of publication bias

Thirty-eight reviews reported assessment of publication bias across 13 major disease areas. The vast majority reported that there was no evidence of publication bias either on visual inspection of funnel plots and/or based on the Begg-Mazumdar and Egger tests. Eight reviews reported some evidence of publication bias; three (Costanzo et al., 2011; Kodama et

al., 2011; Roerecke & Rehm, 2012) related to diseases of the circulatory system, two (Taylor & Rehm, 2012; Zeisser et al., 2013) to external causes of morbidity and mortality, and one each to disease of the eye (Chong et al., 2008), infectious and parasitic diseases (Lönnroth et al., 2008) and neoplasms (Islami et al., 2011). For two reviews of diseases of the circulatory system (Costanzo et al., 2011; Roerecke & Rehm, 2012), omitting studies from the analyses did not have a substantial influence on pooled effect estimates, and in the third review (Kodama et al., 2011) while use of the "trim and fill" procedure attenuated the pooled estimate for heavy alcohol consumption and atrial fibrillation it remained statistically significant. Two reviews, one of fatal motor vehicle injury (Taylor & Rehm, 2012) and one of age-related macular degeneration (Chong et al., 2008) attributed the presence of publication bias to a scarcity of studies reporting small or null effects. Both studies included a low number of studies and use of the tests proposed by Egger and by Begg and Mazumdar are not recommended with fewer than 10 studies (Higgins & Green, 2011). In their review of injury, Zeisser et al. (2013) attributed the presence of publication bias to one study with a large effect size and large standard error; following exclusion of this study the funnel plot no longer showed asymmetry. Two further reviews (Lönnroth et al., 2008; Islami et al., 2011) found evidence of publication bias for studies of heavy alcohol consumption. Both reviews eliminated the studies contributing to publication bias, finding that the subsequent analyses remained quantitatively similar to the main analyses conducted. In their review of oesophageal squamous cell carcinoma, Islami et al. (2011) noted that their findings indicated that 'small study effects' mainly originated from case-control rather than prospective studies.

2.6 Summary of risk estimates information

Tables summarising risk estimates of the relationship between alcohol consumption and the various diseases and health problems examined are presented in Section 3.

3 Summary of risk estimates

3.1 Summary of data from systematic reviews and meta-analyses

Table 2. Summary of risk estimates: All-cause mortality

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates					
		Co	Ca					Group	N	Maximum protection, % (99% CI)	Heterogeneity	Dose-response analysis	Subgroup analyses
Di Castelnuovo et al., 2006	34	-	-	NR	Jpn, UK, Dnk, Pol, Ger, Rus, USA, Swe, Scotland, Fra, Chn, Aus, Ita	94,533	Non-drinkers (excluding former drinkers in 30 curves)	All studies Adjusted (age) Adjusted (age, SES) Adjusted (age, SES, dietary factors) Males Females		19% (17%–20%) 17% (15%–18%) 18% (15%–21%) 18% (12%–24%) 17% (15%–19%) 18% (13%–22%)			Protection was significantly lower in studies that used the category of no alcohol intake and excluded light and/or former drinkers from the reference group. With light and/or former drinkers: 23% (20%–26%) Without light and/or former drinkers: 16% (14%–18%)

Key
Co = cohort studies; Ca = case-control studies; sig = significantly; g/d = grams per day; NA = not applicable; NR = not reported
[a]Arg = Argentina; Aus = Australia; Bel = Belgium; Bgr = Bulgaria; Bls = Belarus; Bra = Brazil; Can = Canada; Chl = Chile; Chn = China; Cri = Costa Rice; Cub = Cuba; Cze = Czech Republic; Dnk = Denmark; Egy = Egypt; Est = Estonia; Eur = Europe (individual countries not specified); Fin = Finland; Fra = France; Ger = Germany; Gmb = Gambia; Gnb = Guinea Bissau; Grc = Greece; Hkg =Hong Kong; Ice = Iceland; Ind = India; Int = International (individual countries not specified); Irn = Iran; Ire = Ireland; Isr = Israel; Ita = Italy; Jam = Jamaica; Jpn = Japan; Kor = Korea; Lva = Latvia; Mex = Mexico; Moz = Mozambique; Mwi = Malawi; Mys = Malaysia; Nzl = New Zealand; Nga = Nigeria; Nor = Norway; Pol = Poland; Pri = Puerto Rico; Rou = Romania; Rus = Russia; SAm = South America (individual countries not specified); Srb/Mne = Serbia and Montenegro; Sgp = Singapore; Spa = Spain; Sud = Sudan; Svn = Slovenia; Swe = Sweden; Swi = Switzerland; Tai = Taiwan; Tha = Thailand; Nld = The Netherlands; Tur = Turkey; Tza = Tanzania; Uga = Uganda; UK = United Kingdom; Uru = Uruguay; USA = United States of America; Vie = Vietnam; Yug = Yugoslavia; Zaf = South Africa.

Table 3. Summary of risk estimates: Overview of conditions

Study details	N studies	Study design		Years	Countries[a]	Reference category	N cases	Pooled risk estimates				
		Co	Ca					Group	N	Effect estimate (95% CI)		
										25 g/d	50 g/d	100 g/d
Bagnardi et al., 2001	229	46	183	NR	NR	Non-drinkers	7,954	Oral cavity	26	1.73 (1.67–1.78)	2.77 (2.67–2.95)	5.75 (5.22–6.34)
							7,239	Oesophagus	28	1.51 (1.48–1.55)	2.21 (2.11–2.31)	4.23 (3.91–4.59)
							4,518	Stomach	16	1.07 (1.04–1.10)	1.15 (1.09–1.22)	1.32 (1.18–1.49)
Cancers							415	Small intestine	2	-	-	-
							5,948	Colon	17	1.14 (1.07–1.21)	1.21 (1.11–1.32)	1.32 (1.16–1.49)
							3,872	Rectum	16	1.11 (1.03–1.20)	1.17 (1.06–1.30)	1.32 (1.16–1.51)
							1,961	Liver	19	1.20 (1.13–1.27)	1.41 (1.26–1.56)	1.83 (1.53–2.19)
							81	Gallbladder	2	-	-	-
							2,524	Pancreas	17	0.98 (0.90–1.05)	1.05 (0.93–1.18)	1.18 (0.94–1.49)
							3,759	Larynx	20	1.35 (1.31–1.40)	1.83 (1.72–1.95)	3.24 (2.89–3.65)
							2,314	Lung	6	1.02 (1.00–1.04)	1.04 (1.00–1.08)	1.08 (1.00–1.18)
							708	Melanoma	2	-	-	-
							44,033	Breast female	49	1.31 (1.27–1.36)	1.67 (1.56–1.78)	2.71 (2.33–3.08)
							242	Cervix	1	-	-	-
							2,473	Endometrium	6	1.05 (0.88–1.24)	1.09 (0.78–1.54)	1.20 (0.60–2.37)
							1,651	Ovary	5	1.11 (1.00–1.24)	1.23 (1.01–1.54)	1.53 (1.03–2.32)
							4,094	Prostate	11	1.05 (1.00–1.08)	1.09 (1.02–1.17)	1.19 (1.03–1.37)
							5,997	Bladder	11	1.04 (0.99–1.09)	1.08 (0.98–1.89)	1.17 (0.97–1.41)
							921	Kidney	2	-	-	-
							14,495	All sites combined	8	1.01 (0.90–1.05)	1.22 (1.11–1.27)	1.91 (1.77–2.06)
Corrao et al., 2004	156	57	99	NR	NR	Non-drinkers	4,507	Oral cavity and pharynx neoplasms	15	1.86 (1.76 –1.96)	3.11 (2.85– 3.39)	6.45 (5.76 –7.24)
							3,233	Oesophagus neoplasms	14	1.39 (1.36 –1.42)	1.93 (1.85– 2.00)	3.59 (3.34 –3.87)
							3,789	Larynx neoplasms	20	1.39 (1.36 –1.42)	1.93 (1.85– 2.00)	3.59 (3.34 –3.87)
15 conditions							5,360	Colon neoplasms	16	1.05 (1.01 –1.09)	1.10 (1.03– 1.18)	1.21 (1.05 –1.39)
							1,420	Rectum neoplasms	6	1.09 (1.08 –1.12)	1.19 (1.14– 1.24)	1.42 (1.30 –1.55)
							1,321	Liver neoplasms	10	1.19 (1.12 –1.27)	1.40 (1.25– 1.56)	1.81 (1.50 –2.19)
							32,175	Breast neoplasms	29	1.25 (1.20 –1.29)	1.55 (1.44– 1.67)	2.41 (2.07 –2.80)
							5,801	Essential hypertension	2	1.43 (1.33 –1.53)	2.04 (1.77– 2.35)	4.15 (3.13 –5.52)
							49,640	Coronary heart disease	28	0.81 (0.79 –0.83)	0.87 (0.84– 0.90)	1.13 (1.06 –1.21)
							893	Ischaemic stroke	6	0.90 (0.75 –1.07)	1.17 (0.97– 1.44)	4.37 (2.28 –8.37)
							1,192	Haemorrhagic stroke	9	1.19 (0.97 –1.49)	1.82 (1.46– 2.28)	4.70 (3.35 –6.59)
							425	Gastroduodenal ulcer	2	0.98 (0.77 –1.25)	0.97 (0.59– 1.57)	0.93 (0.35 –2.45)
							2,202	Liver cirrhosis	9	2.90 (2.71 –3.09)	7.13 (6.35– 8.00)	26.52 (22.26– 31.59)
							247	Chronic pancreatitis	2	1.34 (1.16 –1.54)	1.78 (1.34– 2.36)	3.19 (1.82 –5.59)
							4,501	Injuries and violence	12	1.12 (1.06 –1.18)	1.26 (1.13– 1.40)	1.58 (1.27 –1.95)

Key
Co = cohort studies; Ca = case-control studies; sig = significantly; g/d = grams per day; NA = not applicable; NR = not reported

Table 4. Summary of risk estimates: Individual diseases/health problems

NB: The following table is presented in order of ICD 10 code

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Lönnroth et al., 2008 Tuberculosis	21	3	18	1961-2007	Fin, Can, Ind, Aus, UK, USA, Chn, Est, Mwi, Gnb, Gmb, Lva, Rus.	4,762	No exposure to alcohol	<40 g/day >40 g/day >40 g/day (adjusted[b])	4 11 6	1.08 (0.82–1.40) 3.50 (2.01–5.93) 2.76 (2.09–3.64)	0.82% (<0.01)	NA	No sig. differences across strata explored.
Balinuas et al., 2010a HIV	10	8	2	1996-2007	USA, Aus, Uga, Tza, Tha, Jam, Nld	Not clear	Non-drinkers - lifetime abstainers	Overall Consumption Binge consumption Prior to sex	10 4 5 4	1.98 (1.59–2.47) 1.77 (1.43–2.19) 2.20 (1.29–3.74) 1.87 (1.39–2.50)			No sig. differences across strata explored.
Mao et al., 2010 Bladder cancer	19	6	13	1983-2009	USA, Can, Dnk, Ita, Ger, Nld, Fra, Jpn, Chn	9,284	Not defined	Overall Males Females Beer Wine Spirits	18 10 8 10 10 9	1.00 (0.89–1.10) 0.96 (0.83–1.08) 0.90 (0.60–1.21) 0.86 (0.76–0.96) 0.85 (0.71–1.00) 1.01 (0.87–1.15)	64.9% 72.4% 59.1% 57.0% 78.5% 69.5%	NA	Estimates did not vary from overall findings.
Pelucchi et al., 2012 Bladder cancer	19	16	3	1983-2009	USA, Spa, Ita, Ger, Fra, Nld, Jpn, UK.	11,935	Non-drinkers	<37.5 g/d overall <37.5 g/d males <37.5 g/d females ≥37.5 g/d overall ≥37.5 g/d males	24 11 7 10 5	1.00 (0.92–1.09) 1.09 (0.98–1.22) 0.91 (0.76–1.09) 1.02 (0.72–1.33) 1.52 (0.99–2.33)	42.3% 25.1% 41.4% 67.7% 65.0%	NA	No study had a notable influence on the overall estimate.
Key et al., 2006 Breast cancer	98	21	77	1982-2003	Aus, Bra, Can, Chl, Dnk, Fin, Fra, Ger, Grc, Nld, Ita, Jpn, Kor, Nzl, Nga, Pol, Rus, Spa, Swe, Nor, UK, USA, Isr, Uru	136,381	Non-drinkers	Overall Sensitivity I[c] Beer Wine Spirits	89 19 30 32 31	1.11 (1.06–1.17) 1.22 (1.09–1.37) 1.16 (1.04–1.29) 1.14 (1.05–1.24) 1.14 (1.06–1.23)		% excess risk per 10 g/day: 12% (9%–15%)	Retrospective studies with hospital controls associated with sig. higher risk estimates than community controls
Fedirko et al., 2011 Colorectal cancer	61	27	34	1986–2010	Jpn, Kor, Chn, Hkg, Sgp, Aus, USA, Can, Fra, Ita, Swe, Nld, Dnk, UK, Fin, Eur	42,644	Non-drinkers or occasional alcohol drinkers	Overall Colon Rectum Male Female ≤12.5 g/d ≤12.5 g/d male ≤12.5 g/d female >12.5 to <50 g/d >12.5 to <50 g/d male >12.5 to <50 g/d female ≥50 g/d ≥50 g/d male ≥50 g/d female	57 42 38 33 26 43 27 25 53 32 21 19 15 2	1.12 (1.06–1.19) 1.05 (0.99–1.12) 1.19 (1.09–1.31) 1.25 (1.13–1.39) 1.00 (0.94–1.07) 1.00 (0.95–1.05) 1.02 (0.92–1.14) 0.95 (0.89–1.01) 1.21 (1.13–1.28) 1.24 (1.13–1.37) 1.08 (1.03–1.13) 1.52 (1.27–1.81) 1.62 (1.31–2.01) 1.54 (1.04–2.29)		10 g/d = 1.07 (1.04–1.10); 25 g/d =1.18 (1.12–1.25); 50 g/d =1.38 (1.28–1.50); 100 g/d =1.82 (1.41–2.35)	Factors explored in analyses were not sources of heterogeneity.

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Sun et al., 2011 Endometrial cancer	20	6	14	1986-2009	USA, Swe, Can, Nld, Ita, Chn, Grc, Jpn	7,638	Non-drinkers	Cohort Case-control Case-control Beer Wine Liquor	6 14 10 7 7 7	1.04 (0.91–1.18) 0.89 (0.76–1.05) 0.90 (0.80–1.00 0.91 (0.75–1.11) 1.07 (0.92–1.25) 1.22 (1.03–1.45)	(NS) (p<0.001) (NS)		Majority heterogeneity accounted for in 4 case-control studies. Sensitivity analyses did not show any sig. differences in summary estimates.
Kan et al., 2011 Extrahepatic bile system cancer	10	1	9	1987–2009	USA, Can, Jpn, Nld, Aus, Pol, Fra, Ger, Ita, Swe, Irn	113,767 [d]	Non-drinkers and low drinkers	Overall Case-control >80 g/d	10 9 3	0.82 (0.72–0.94) 0.80 (0.68–0.93) 1.58 (0.97–2.57)	27.2% 29.6% (0.06)		
Tramacere et al., 2012a Gastric cancer	59	15	44	1963-2010	Jpn, USA, Ice, Svn, Fra, Chn, Ita, Uru, Tur, Tai, Spa, Ind, Pol, Swe, Rus, Bra, UK, Tha, Vie, Dnk, Nor, Kor, Nld	34,557	Non-drinkers and occasional drinkers	Overall Case–control Cohort Gastric cardia Gastric noncardia >50 g/d	59 44 15 12 14 13	1.07 (1.01–1.13) 1.08 (1.00–1.18) 1.04 (0.97–1.11) 0.94 (0.78–1.13) 1.07 (0.91–1.26) 1.20 (1.01–1.44)	52.0% (0.00) 56.6% (0.00) 31.2% (0.11) 29.7% (0.16) 65.9% (0.00) 58.9% (0.00)	10 g/d =0.95 (0.91–0.99); 25 g/d =1.01 (0.96–1.06); 50 g/d = 1.14 (1.08–1.21); 75 g/d = 1.30 (1.19–1.40); 100 g/d =1.45 (1.31–1.62); 125 g/d =1.62 (1.42–1.85)	No sig. differences across strata of sex, geographic area or studies with and without adjustment for smoking and fruit and vegetable consumption.
Tramacere et al., 2012b Hodgkin lymphoma	10	2	8	2006-2009	Ita, Cze, Fra, Ire, Spa, Ger, UK, Can, Jpn, USA	1,488	Non-drinkers	Overall ≤12.5 g/d >12.5 g/d	10 7 8	0.70 (0.60–0.81) 0.71 (0.57–0.89) 0.73 (0.60–0.87)	0.0% (0.48) 11.7% (0.34) 0.0% (0.85)	Inverse, but not significant; 10 g/d = 0.95 (0.89–1.02); 20 g/d = 0.87 (0.72–1.05); 30 g/d = 0.82 (0.64–1.04)	Plot suggested absence of publication bias, no asymmetry.
Islami et al., 2010 Laryngeal cancer	40	2	38	1956-2009	USA, UK, Can, Dnk, Uru, Fra, Ita, Spa, Swi, Kor, Chn, Tur, Ger, Tai, Bel, Eur	9,351	Non-drinkers and occasional drinkers	Overall Adjusted ≤12.5 g/d Adjusted >12.5 to <50 g/d Adjusted ≥50 g/day Adjusted	40 20 12 6 35 20 33 17	1.90 (1.59–2.28) 1.84 (1.50–2.26) 0.88 (0.71–1.08) 0.88 (0.70–1.12) 1.47 (1.25–1.72) 1.50 (1.23–1.83) 2.62 (2.13–3.23) 2.46 (1.88–3.22)	85.8% (<0.001) 81.5% (<0.001) 24.8% (0.19) 22.6% (0.26) 66.7% (0.001) 64.2% (0.001) 81.4% (0.001) 79.7% (0.001)	12.5 g/d = 1.20 (1.15–1.25); 25 g/d = 1.45 (1.33–1.57); 37.5 g/d = 1.72 (1.52–1.90); 50 g/d = 2.04 (1.76–2.36); 100 g/d = 3.77 (2.93–4.86)	Results did not differ from overall analyses. Estimates based on non-drinkers only as the ref. group did not differ from the overall results
Bagnardi et al., 2011 Lung cancer	10	4	6	1988-2010	USA, Ita, Can, Jpn, Nld, Pol, Chn, Eur	1,913	Non-drinkers	Overall Male Female Case–control Cohort	10 4 6 6 4	1.21 (0.95–1.55) 1.22 (0.83–1.80) 1.26 (0.81–1.95) 1.25 (0.68–2.31) 1.02 (0.92–1.28)	77% 51% 86% 86% 31%	Increase in 10 g/d = 1.01 (0.92–1.10)	No sig. differences across strata explored.

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Tramacere et al., 2011 Oesophageal and gastric cardia AC	24	4	20	1989-2010	Jpn, USA, Chn, Grc, Uru, Swe, Rus, Rou, Cze, Pol, Ire, Aus, UK, Nld	5,500	Non-drinkers or occasional drinkers	Any intake ≤12.5 g/d >12.5 to <50 g/d ≥50 g/d Case-control Cohort Oesophageal AC Gastric cardia	24 15 16 13 20 4 13 15	0.96 (0.85–1.09) 0.86 (0.75–0.99) 0.90 (0.73–1.10) 1.16 (0.92–1.46) 0.99 (0.83–1.17) 0.96 (0.85–1.09) 0.87 (0.74–1.01) 0.89 (0.76–1.03)	49.2% (0.003) 55.7% (0.001) 0.0% (0.60) 35.7% (0.10) 24.9% (0.18)	No sig. increased risk at any level; nadir = 25 g/day; RR<1 up to 70 g/day. Risk estimates for higher doses not sig.	No sig. differences across strata explored.
Tramacere et al., 2010 Oral and pharyngeal cancer	45	2	43	1957-2008	USA, Pri, Can, Fra, Ita, Chn, Kor, Uru, Dnk, Ger, Jpn, Spa, Cub, Grc, Ind, Pol, Swi, Tai, Swe, Srb/Mne, Eur	17,085	Non-drinkers or occasional drinkers	≤12.5 g/d ≥50 g/d	20 31	1.21 (1.10–1.33) 5.24 (4.36–6.30)	(0.71) (<0.01)	10 g/d = 1.29 (1.25–1.32); 25 g/d = 1.85 (1.74–1.96); 50 g/d = 3.24 (2.89–3.64); 75 g/d = 5.42 (4.58–6.40); 100 g/d = 8.61 (6.91–10.73); 125 g/d = 13.02 (9.87–17.18)	No sig. differences across strata explored.
Rota et al., 2012 Epithelial ovarian cancer	27	4	23	1983-2012	USA, Grc, Jpn, Ita, Ind, Can, Swe, Tai, Aus, Kor, UK, UK, Int	16,554	Non-drinkers or occasional drinkers	Overall ≤12.5 g/d >12.5 to <37.5g/d ≥37.5 g/d	27 20 16 4	1.00 (0.95–1.05) 0.97 (0.92–1.02) 1.03 (0.96–1.11) 1.09 (0.80–1.50)	8.8% (0.33) 14.6% (0.27) 22.4% (0.20) 46.7% (0.13)	Meta-regression models indicated a lack of a dose–risk relationship.	No sig. differences across strata explored.
Tramacere et al., 2010 Pancreatic cancer	32	11	21	1983-2009	USA, Jpn, Swe, Fra, UK, Swi. Aus, Grc, Chn, Ita, Can, Fin, Nld, Int	13,728	Non-drinkers and occasional drinkers	Overall Females Males >37.5 g/day Females Males	32 12 16 13 6 11	0.92 (0.86–0.97) 0.89 (0.85–0.93) 0.95 (0.86–1.11) 1.22 (1.12–1.34) 1.16 (0.94–1.44) 1.19 (1.05–1.33)	(0.06)	NA	Sig. association in: cohort studies (cohort 1.29 [1.15–1.45] vs. case-control 1.10 [0.97–1.25]); studies reporting estimates adjusted for tobacco smoking (adjusted 1.23 [1.12–1.35] vs. non-adjusted 1.09 [0.90–1.32]). Estimates based on non-drinkers only as the reference group did not differ from the overall results
Rota et al., 2011 Prostate cancer	72	22	50	1971-2010	USA, Jpn, Zaf, Chn, Nld, Uru, Swe, UK, Ind, Can, Grc, Tai, Ita, Aus, Chl, Nzl, Ger, Nor, Dnk, Fin, Eur	52,899	Non-drinkers and occasional drinkers	Overall Adjusted ≤12.5 g/d Light adjusted >12.5 to <50 g/d Adjusted ≥50 g/d Adjusted	72 17 36 12 40 11 17 4	1.06 (1.01–1.10) 1.11 (1.04–1.18) 1.05 (1.02–1.08) 1.06 (1.02–1.10) 1.06 (1.01–1.11) 1.10 (1.03–1.18) 1.08 (0.97–1.20) 1.19 (1.13–1.26)	39.0% (0.001) 36.7% (0.07) 0.0% (0.70) 0.0% (0.67) 29.9% (0.04) 33.3% (0.13) 40.6% (0.04) 0.0% (0.51)	10 g/day = 1.02 (1.00–1.04); 25 g/ day = 1.05 (1.01–1.09); 50 g/day = 1.09 (1.02–1.16); 100 g/day = 1.12 (0.97–1.30)	Results consistent with the overall findings.

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Bellocco et al., 2012 Renal cell carcinoma	20	5	15	1986-2011	USA, Can, Fra, Dnk, Swe, Ita, Jpn, UK, Kor, Eur, Int	12,481	Non-drinkers	Overall Men Women <12.5 g/d ≥12.5 to <50 g/d ≥50 g/d	20 14 12 14 13 5	0.85 (0.80–0.92) 0.88 (0.78–0.98) 0.79 (0.72–0.86) 0.90 (0.84–0.97) 0.79 (0.71–0.88) 0.89 (0.58–1.39)	45.4% (0.005) 32.1% (0.08) 43.1% (0.03) 63.7% (0.02)	12 g/day = 0.84 (0.79–0.90); 32 g/day = 0.68 (0.59–0.78); 50 g/day = 0.60 (0.50–0.73); 100 g/day = 0.61 (0.39–0.95)	Did not differ from the overall findings.
Song et al., 2012 Renal cell cancer	24	4	20	1974-2011	USA, Fra, Can, Aus, Dnk, Swe, Ger, Ita, Rus, Rou, Pol, Cze, Fin, Nld, UK	13,819 renal cell 1,537 kidney	Non-drinkers or occasional drinkers	Overall Case-control Cohort Beer Wine Liquor	22 18 4 12 12 12	0.73 (0.67–0.79) 0.76 (0.68–0.85) 0.73 (0.67–0.79) 0.81 (0.70–0.91) 0.75 (0.59–0.91) 0.76 (0.66–0.87)	7.9% (0.34) 14.7% (0.25) 0.0% (0.60) (0.26) (<0.001) (0.12)	Significant non-linearity for the overall association; risk attenuated > ~15 g/d.	Stronger inverse association in cohort studies (vs. case–control p=0.02) and more recent studies (data NR).
Chen et al., 2008 Nasopharyn-geal carcinoma	14	0	14	1976-2001	USA, Sgp, Hkg, Mys, Tai, Tha	3,486	Non-drinker or light intake	Overall Adjusted (smoking)	11 6	1.33 (1.09–1.62) 1.26 (0.99–1.62)	17.1% (0.28)	Inverse association up to ~29 g/day with risk increasing with higher intake.	Studies controlling for smoking and studies conducted in China had a weaker association.
Islami et al., 2011 Oesophageal squamous cell carcinoma	53	13	40	1961-2010	USA, Pri, Fra, Uru, Dnk, Kor, Hkg, Jpn, Chn, Grc, SAm Ita, Swe, UK, Ger, Tha, Ind, Tai, Eur, Spa, Aus, Can	9,826	Non-drinkers or occasional drinkers	<12.5 g/d Adjusted ≥12.5 to <50 g/d Adjusted ≥50 g/d Adjusted	26 19 47 28 39 21	1.31 (1.10–1.57) 1.38 (1.14–1.67) 2.27 (1.89–2.72) 2.62 (2.07–3.31) 4.89 (3.84–6.23) 5.54 (3.92–7.82)	56.2% (0.001) 51.5% (0.002) 85.3% (0.001) 82.8% (0.001) 87.1% (0.001) 89.9% (0.001)	NA	Similar to overall analysis, except for geographic region (stronger association for light intake in Asian countries).
Baliunas et al., 2010b Type II diabetes	20			1988-2007	USA, Nld, Fin, Aus, Kor, Ger, Jpn, UK	12,556	Lifetime and current abstainers					Males: nadir 22 g/day: RR 0.87 (0.76–1.00); deleterious >60 g/day: RR 1.01 (0.71–1.44) Females: nadir 24 g/day: RR 0.60 (0.52–0.69); deleterious >50 g/day: RR 1.02 (0.83–1.26)	
Anstey et al., 2009 Dementia	15	15	0		Not clear	Not clear	Non-drinkers	Any intake Alzheimer disease Any dementia Cognitive decline Light to moderate intake Alzheimer disease Vascular dementia Any dementia Heavy intake Alzheimer disease Vascular dementia Any dementia	 2 4 2 6 4 7 4 3 4	 0.66 (0.47–0.94) 0.66 (0.53–0.82) 0.28 (0.03–2.83) 0.70 (0.39–1.26) 0.75 (0.57–0.98) 0.74 (0.61–0.91) 0.92 (0.59–1.45) 1.36 (0.68–2.71) 1.04 (0.69–1.56)	 (NS) (NS) (0.00) (0.04) (NS) (NS) (NS) (NS) (NS)	NA	NA; some discussion of former drinkers vs. lifetime abstainers but not explored in meta-analysis

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Samokhvalov et al., 2010 Epilepsy	6	0	6	1987-2003	Chn, Ita, Nga, USA	934	Non-drinkers	Overall <50 g/d	6 4	2.19 (1.83–2.63) 1.29 (1.03–1.61)	9.0% (0.36) 0.0% (0.84)	12 g/d = 1.17 (1.13–1.21); 48 g/d = 1.81 (1.59–2.07) ; 72 g/d = 2.44 (2.00–2.97); 96 g/d = 3.27 (2.52–4.26)	NA
Chong et al., 2008 Age-related macular degeneration	5	5	0	1999-2007	USA, Dnk, Ice	1,923	Not clear[e]	Early AMD Late AMD	5 4	1.47 (1.10–1.95) Not pooled	30.9% (0.01)	NA	NA
Kodama et al., 2011 Atrial fibrillation	14	9	5	1985-2008	USA, Can, Swe, Dnk, Spa, Swi	7,558	Not clear[e]	Overall vs. non-drinkers	14 8	1.51 (1.31–1.74) 1.36 (1.18–1.57)	45.8% (0.02) 44.6% (0.08)	Increase in risk per 10 g/d: 1.08 (1.05–1.10)	Results consistent with the overall findings
Samokhvalov et al., 2010 Atrial fibrillation	6	5	1	1987-2008	UK, USA, Fin, Dnk	4,767	Non-drinkers	>0 to 24 g/d >24 to 36 g/d >36 to 48 g/d >48 g/d >0 to 24 g/d female >24 to 36 g/d female >36 to 48 g/d female >48 g/d female >0 to 24 g/d male >24 to 36 g/d male >36 to 48 g/d male >48 g/d male	- - - - - - - - - - - -	1.00 (0.92–1.09) 1.11 (0.98–1.25) 1.22 (1.02–1.46) 1.50 (1.22–1.85) 0.99 (0.91–1.07) 1.17 (1.01–1.36) 1.17 (0.84–1.65) 2.18 (1.38–3.43) 1.02 (0.90–1.16) 1.09 (0.94–1.26) 1.25 (1.01–1.55) 1.53 (1.23–1.91)	- - - - - - - - - - - -	Females: 24 g/d = 1.07 g/d (1.04– 1.10), 60 g/d 1.42 (1.23–1.64); 120 g/d 2.02 (1.60–2.97) Males: 24 g/d = 1.08 (1.04–1.11); 60 = 1.44 (1.23–1.69); 120 g/d = 2.09 (1.52–2.86)	NA
Roerecke & Rehm, 2011 Ischaemic heart disease	44	32	12	1980-2010	USA, Nzl, Jpn, UK, Aus, Swe, Dnk, Bgr, Ita, Fra, Fin, Cri, Chn, Spa	38,627	Lifetime abstainer	Mortality <2.5 g/day male 2.5 to <12 g/d male 12 to <24 g/d male 24 to <36 g/d male <2.5 g/day female 2.5 to <12 g/d female 12 to <24 g/d female 24 to <36 g/d female Morbidity <2.5 g/day male 2.5 to <12 g/d male 12 to <24 g/d male 24 to <36 g/d male <2.5 g/day female 2.5 to <12 g/d female 12 to <24 g/d female 24 to <36 g/d female	 5 17 12 11 3 8 7 5 3 9 8 3 2 5 5 3	 0.94 (0.74–1.21) 0.89 (0.79–1.00) 0.86 (0.73–1.02) 0.78 (0.63–0.97) 0.98 (0.74–1.30) 0.84 (0.74–0.96) 1.03 (0.84–1.27) 0.89 (0.57–1.40) 0.82 (0.65–1.02) 0.77 (0.65–0.92) 0.75 (0.64–0.88) 0.74 (0.53–1.02) 0.91 (0.78–1.07) 0.54 (0.45–0.65) 0.61 (0.38–0.99) 0.40 (0.14–1.13)	 37% (0.18) 65% (<0.001) 72% (<0.001) 76% (<0.001) 58% (0.10) 23% (0.24) 3% (0.40) 48% (0.10) 15% (0.31) 68% (0.001) 42% (0.08) 65% (0.06) 0% (0.49) 0% (0.95) 70% (0.009) 84% (0.002)	Stratified only (24 studies) Mortality Males: nadir 32 g/d; reversion point 63 g/d. Females: nadir 11 g/d; reversion point 31 g/d Morbidity Males: nadir 69 g/d; no reversion point. Females: nadir 14 g/d; reversion point 57 g/d. NB: Heterogeneity was highly statistically significant in most models.	Omitting studies individually did not reveal any substantial influence of any particular study on the pooled effect estimates. None of the interaction terms examined explained the heterogeneity in the models, except age at time of IHD event (<65 years vs. >65 years) in women

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Roerecke & Rehm, 2010 Ischaemic heart disease (heavy drinking occasions)	14	10	4	1982-2007	Dnk, Fin, USA, Can, Rus, UK, Yug, Cri, Aus, Swe	3,808	Regular moderate drinking	Overall	14	1.45 (1.24–1.70)	53.9% (0.008)	NA	Factors examined in meta-regression model did not result in statistical significance. Omitting each study separately resulted in random variation around the overall estimate
Taylor et al., 2009 Hypertension	12	12	0	1989-2006	USA, Kor, Jpn	NR	Lifetime abstainer	Risk increase per 10 g/d Males Females	 9 9	 1.09 (1.07–1.12) 1.10 (1.06–1.14)	 0.0% (0.509) 75.0% (0.000)	Males: linear relationship Females: 'J-shaped' nadir 4 g/d, reversion point 15 g/d	Suggested that Asian populations may have an increased risk of hypertension compared to the non-Asian populations.
Patra et al., 2010 Ischaemic stroke (IS); Haemorrhagic stroke (HS)	26	17	9	1986-2009	USA, Jpn, Fin, Kor, Chn, UK, Spa, Aus	14,418	Lifetime abstainers	Haemorrhagic stroke Mortality males Morbidity males Mortality females Morbidity females Ischaemic stroke Mortality males Morbidity males Mortality females Morbidity females	 12 11 6 5 11 16 5 9	 1.11 (1.06–1.15) 1.12 (1.06–1.19) 1.21 (1.07–1.38) 1.14 (1.03–1.27) 1.04 (1.01–1.07) 1.04 (1.02–1.07) 1.04 (1.01–1.08) 1.05 (1.01–1.08)	 40% (0.006) 56% (0.000) 24% (0.179) 53% (0.005) 10% (0.297) 35% (0.007) 10% (0.344) 43% (0.010)	Mortality Males: linear relationship. Females: 'J-shaped'. Inverse association ≤12 g/d. Morbidity Males: linear relationship. Females: 'J-shaped'. nadir 12 g/d (0.69; 0.54–0.89); reversion point 36 g/d; Mortality Males: 'J-shaped'. nadir 12 g/d; reversion point 35 g/d Females: 'J-shaped'. nadir 12 g/d; reversion point 44 g/d. Morbidity Males: 'J-shaped'. reversion point 37 g/d Females: 'J-shaped'. reversion point 46 g/d	

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Samokhvalov et al., 2010 Pneumonia	5	2	3	1994-2008	Fin, Spa, USA	2,371	Non-drinkers					24 g/d = 1.12 (1.02–1.23), 60 g/d = 1.33 (1.06–1.67); 120 g/d = 1.76 (1.13–2.77)	NA
Rehm et al., 2010 Liver cirrhosis	17	14	3	1980-2003	USA, Jpn, Ita, Dnk, Chn,	3,384	Lifetime abstainers	Mortality >0 to 12 g/d females >12 to 24 g/d females >24 to 36 g/d females >36 to 48 g/d females >48 to 60 g/d females >60 g/d females >0 to 12 g/d males >12 to 24 g/d males >24 to 36 g/d males >36 to 48 g/d males >48 to 60 g/d males >60 g/d males Morbidity >0 to 12 g/d females >12 to 24 g/d females >24 to 36 g/d females >36 to 48 g/d females >48 to 60 g/d females >60 g/d females >0 to 12 g/d males >12 to 24 g/d males >24 to 36 g/d males >36 to 48 g/d males >48 to 60 g/d males >60 g/d males	 - - - - - - - - - - - - - - - - - - - - - - - - -	 1.9 (1.1–3.1) 5.6 (4.5–6.9) 7.7 (6.3–9.5) 10.1 (7.5–13.5) 14.7 (11.0–19.6) 22.7 (17.2–30.1) 1.0 (0.6–1.6) 1.6 (1.4–2.0) 2.8 (2.3–3.4) 5.6 (4.5–7.0) 7.0 (5.8–8.5) 14.0 (11.7–16.7) 0.4 (0.1–1.2) 1.0 (0.5–1.9) 2.4 (1.8–3.2) 1.9 (1.8–3.2) 5.9 (3.7–9.3) 6.1 (3.9–6.4) 0.3 (0.1–0.9) 0.3 (0.2–0.4) 0.7 (0.5–1.0) 2.0 (1.5–2.7) 2.3 (1.7–3.2) 5.0 (3.9–6.4)		Continuous dose–response relationship between alcohol consumption and risk of liver cirrhosis in both mortality and morbidity studies. Mortality Females: 24 g/d = 4.9 (4.0–6.2); 60 g/d = (8.8–17.7) Morbidity Females: 24 g/d = 3.2 (2.6–3.9); 60 g/d = 6.2 (4.4–8.7). Similar pattern for males (data NR).	
Irving et al., 2012 Pancreatitis	6	2	4	1999-2008	Ita, Jpn, Swe, USA, Dnk	1,671	Non-drinkers	>0 to 24 g/d >24 to 48 g/d >48 g/d	- - -	1.0 (0.8–1.2) 1.2 (1.0–1.5) 2.5 (2.0–3.1)		36 g/d = 1.2 (1.2–1.3); 96 g/d = 4.2 (3.1–5.7)	
Zhu et al., 2012 Psoriasis	15	0	15	2002-2011	USA, Sgp, Fra, Swe, Chn, Mne, Nld, Swi, Ita, Spa, Ger, Tur	7,681	Non-drinkers	Overall 1–20 drinks/month[f] ≥20 drinks/month[f]	15 3 3	1.53 (1.16–2.01) 1.50 (0.72–3.09) 1.94 (0.97–3.86)	92.2% (0.000) (0.000) (0.000)	NA	Limited discussion of heterogeneity. Omitting studies from the analysis did not materially alter the results.
Berg et al., 2008 Hip fracture	13	8	5	1988-2007	NR	4,293	Non-drinkers	>0 to 7 g/d >7 to 14 g/d >14 to 28 g/d >28 g/d	5 10 9 5	0.84 (0.70-1.01) 0.80 (0.71-0.91) 0.91 (0.76–1.09) 1.39 (1.08–1.79)			Heterogeneity not reported or discussed. Reference category discussed but not explored in analyses.

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Parsons & Im, 2009 Benign prostatic hyperplasia	19	-	-	1985-2008	NR	NR	Not clear[g]	>0 to 5 g/d >5 to 12 g/d >12 to 15 g/d >15 to 24 g/d >24 to 36 g/d >36 g/d	5 8 5 3 7 6	0.90 (0.80–1.01) 0.86 (0.79–0.94) 0.66 (0.54–0.81) 0.82 (0.69–0.97) 0.78 (0.69–0.88) 0.65 (0.58–0.74)	(0.23) (0.02) (0.008) (0.02) (<0.001) (<0.001)		No sig. differences across strata explored. No discussion of impact of reference category.

Key
AC = adenocarcinoma; Co = cohort studies; Ca = case-control studies; sig = significantly; g/d = grams per day; NA = not applicable; NR = not reported
[a]Arg = Argentina; Aus = Australia; Bel = Belgium; Bgr = Bulgaria; Bls = Belarus; Bra = Brazil; Can = Canada; Chl = Chile; Chn = China; Cri = Costa Rice; Cub = Cuba; Cze = Czech Republic; Dnk = Denmark; Egy = Egypt; Est = Estonia; Eur = Europe (individual countries not specified); Fin = Finland; Fra = France; Ger = Germany; Gmb = Gambia; Gnb = Guinea Bissau; Grc = Greece; Hkg =Hong Kong; Ice = Iceland; Ind = India; Int = International (individual countries not specified); Irn = Iran; Ire = Ireland; Isr = Israel; Ita = Italy; Jam = Jamaica; Jpn = Japan; Kor = Korea; Lva = Latvia; Mex = Mexico; Moz = Mozambique; Mwi = Malawi; Mys = Malaysia; Nzl = New Zealand; Nga = Nigeria; Nor = Norway; Pol = Poland; Pri = Puerto Rico; Rou = Romania; Rus = Russia; SAm = South America (individual countries not specified); Srb/Mne = Serbia and Montenegro; Sgp = Singapore; Spa = Spain; Sud = Sudan; Svn = Slovenia; Swe = Sweden; Swi = Switzerland; Tai = Taiwan; Tha = Thailand; Nld = The Netherlands; Tur = Turkey; Tza = Tanzania; Uga = Uganda; UK = United Kingdom; Uru = Uruguay; USA = United States of America; Vie = Vietnam; Yug = Yugoslavia; Zaf = South Africa.
[b]Exclusion of studies with highest SE and two studies with the highest and lowest effect sizes
[c]Multivariate adjusted odds ratio and quality score of 3.
[d]Unclear whether number of cases or overall sample size.
[e]Highest alcohol consumption categories compared with the lowest.
[f]Not defined in grams per day.
[g]Assumed non-drinkers and occasional drinkers.

Table 5. Summary of risk estimates: Injury

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Taylor et al., 2010 Injury	28	0	21[b]	1983-2008	Aus, Fin, Mex, USA, Can, USA, Nzl, Ger, Pol, Arg, Bls, Bra, Chn, Cze, Ind, Mex, Moz, Zaf, Swe, Swi	28,825	NA	10 g/d increase All injury Intentional injury Falls Motor vehicle accidents Other unintentional	 20 5 5 8 13	 1.30 (1.27–1.34) 1.38 (1.22–1.55) 1.25 (1.14–1.36) 1.24 (1.18–1.31) 1.32 (1.27–1.36)	51% (<0.0001)	Non-linear relationship = intentional injury, motor vehicle accidents, other unintentional injuries Linear relationship = falls	Case–control studies presented lower overall risks than case–crossover studies (p = 0.02).
Taylor et al., 2012 Fatal motor vehicle accidents	5	0	5	1993-2004	USA, Aus, Nzl	6,038	NA	0.02% increase in BAC	5	1.74 (1.43–2.14)	99.4% (<0.0001)	At 0.02% BAC (~12 g): OR = 3.64 (3.37–3.94) At 0.08% BAC (i.e. legal limit): OR = 13.0 (11.1–15.2)	Results of analyses were not statistically sig. different from the main meta-analysis.
Zeisser et al., 2013	14			1988-2009	Aus, USA, Mex, Swi, Pol, Can, Ita, Arg, Bls, Bra, Cze, Nzl, Swe, Ind[c]	22,182[d]	No alcohol intake	Injury arising within 6 h Overall Females Males Case-crossover ED case-control Population case-control	 14 5 6 5 5 4	 2.80 (2.21–3.54) 2.29 (1.36–3.84) 1.07 (0.72–1.61) 3.82 (2.65–5.50) 1.98 (1.39–2.82) 3.15 (1.58–6.25)			Significant differences in OR magnitude when comparing studies by design and by recall period. Studies that provided gender-specific estimates found a large and significant overall effect for females, but a small and non-significant effect for males.

Key
BAC = blood alcohol concentration; Co = cohort studies; Ca = case-control studies; ED = emergency department; sig = significantly; g/d = grams per day; NA = not applicable; NR = not reported
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[b]Seven studies used a case-crossover design.
[c]Results for India were later excluded given strong evidence of publication bias.
[d]Includes 556 cases from India later excluded.

Table 6. Summary of risk estimates: Pregnancy

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Latino-Martel et al., 2010 Acute lymphoblastic leukaemia (ALL); Acute myeloid leukaemia (AML)	21	0	21	1985-2009	Nld, USA, Can, Aus, Grc, Ger, Ita, Egy, Bra, Chl, Chn, Hkg, Jpn, Mex, Fra, Cri, Tai	8,128	No alcohol intake in pregnancy	ALL Overall Beer Wine Spirits AML Overall Beer Wine Spirits	 11 5 5 6 9 4 4 4	 1.10 (0.93–1.29) 1.04 (0.77-1.40) 1.02 (0.79-1.32) 1.29 (1.05-1.59) 1.56 (1.13–2.15) 1.18 (0.79-1.75) 1.67 (1.21-2.32) 1.62 (0.68-3.81)	 (0.001) (0.09) (0.04) (0.31) (0.03) (0.63) (0.87) (0.03)	Risk increase per drink[b]: GL (4 studies) = 1.02 (0.95-1.09) ALL (5 studies) = 1.04 (0.97–1.12) AML (3 studies) = 1.24 (0.94–1.64)	Factors examined in subgroup analyses did not substantially change the risk estimates.
Patra et al., 2011 Low birth weight, preterm birth and small for gestational age (SGA)	36	-	-	NR	NR	20,582 low birth-weight; 12,888 preterm births; 8,679 SGA	Non-drinkers	Low birth weight Adjusted Preterm birth Adjusted SGA Adjusted	28 16 21 10 11 8	1.12 (1.04–1.20) 1.06 (0.99–1.13) 1.03 (0.91–1.16) 0.93 (0.86–1.01) 1.11 (0.95–1.30) 0.99 (0.89–1.10)	80% (<0.001) 62% (<0.001) 89% (<0.001) 64% (<0.001) 92% (<0.001) 82% (<0.001)	Low birth weight: Risk not apparent until >10 g/d; linearly associated up to 120 g/d. Preterm birth: No risk associated with <19 g/d; increased risk at an average of 36 g/d. SGA: No risk associated with <10 g/d; increased risk at an average of 36 g/day.	Study type affected the risk estimate for preterm birth.

Key
ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; Co = cohort studies; Ca = case-control studies; sig = significantly; g/d = grams per day; NA = not applicable; NR = not reported; SGA = small for gestational age
[a]Arg = Argentina; Aus = Australia; Bel = Belgium; Bgr = Bulgaria; Bls = Belarus; Bra = Brazil; Can = Canada; Chl = Chile; Chn = China; Cri = Costa Rice; Cub = Cuba; Cze = Czech Republic; Dnk = Denmark; Egy = Egypt; Est = Estonia; Eur = Europe (individual countries not specified); Fin = Finland; Fra = France; Ger = Germany; Gmb = Gambia; Gnb = Guinea Bissau; Grc = Greece; Hkg =Hong Kong; Ice = Iceland; Ind = India; Int = International (individual countries not specified); Irn = Iran; Ire = Ireland; Isr = Israel; Ita = Italy; Jam = Jamaica; Jpn = Japan; Kor = Korea; Lva = Latvia; Mex = Mexico; Moz = Mozambique; Mwi = Malawi; Mys = Malaysia; Nzl = New Zealand; Nga = Nigeria; Nor = Norway; Pol = Poland; Pri = Puerto Rico; Rou = Romania; Rus = Russia; SAm = South America (individual countries not specified); Srb/Mne = Serbia and Montenegro; Sgp = Singapore; Spa = Spain; Sud = Sudan; Svn = Slovenia; Swe = Sweden; Swi = Switzerland; Tai = Taiwan; Tha = Thailand; Nld = The Netherlands; Tur = Turkey; Tza = Tanzania; Uga = Uganda; UK = United Kingdom; Uru = Uruguay; USA = United States of America; Vie = Vietnam; Yug = Yugoslavia; Zaf = South Africa.
[b]Not defined in grams per day.

Table 7. Summary of risk estimates: Narrative systematic reviews

Study details	N studies	Years	Countries[a]	Narrative synthesis findings	
				Main findings	**Subgroup findings/ Notes**
Bay & Kesmodel, 2011	39	1980-2008	NR	Findings generally suggested a negative effect when maternal alcohol consumption exceeded 4 drinks/day (equivalent to 48 g/day). Studies of the effect of alcohol consumption between 10 to 30 drinks/week (equivalent to 120-360 g/week) showed inconsistent results. Lack of evidence on the effects of binge drinking on motor development.	NA
Henderson et al., 2007a	46	NR	NR	*Outcomes* / *N* / *Results* Miscarriage / 8 / 5 studies found significant increase; RRs = 2.0–3.79, OR = 1.1 Stillbirth / 5 / 1 study found significant increase at 25–60 g/week, OR 7.6 Impaired growth / 7 / 1 study found significant increase Birthweight / 19 / 1 study found a significant increase Preterm birth / 16 / 1 study found a significant increase Malformations / 6 / 1 study found a significant increase	Authors note that many of the reported studies had methodological weaknesses.
Henderson et al., 2007b	14	NR	USA, UK, Aus, Dnk, Can	*Outcomes* / *N* / *Results* Birthweight, gestational age & growth / 7 / 3 studies found an association Birth defects / 3 / Inconsistent evidence Neurodevelopment / 4 / Effects generally quite small but reported across all studies.	Authors note that many of the reported studies had methodological weaknesses despite being assessed as having reasonable quality. Difficult to separate out the effect of binge-drinking from heavy drinking.
McCambridge et al., 2011	54	1983-2008	USA, Swe, UK, Nzl, Aus, Fin, Nld	Consistent evidence that higher alcohol consumption in late adolescence continues into adulthood and is also associated with alcohol problems including dependence. Evidence from a single population-based cohort that late adolescent drinking can cause early death among men, principally through car crashes and suicides. Apparent effects of late adolescent drinking may persist beyond the age of 30.	Authors note that uncontrolled confounding means there is uncertainty about long term effects and that the existing evidence is generally of insufficient quality to warrant causal inferences.
Kool et al., 2009	8	1983-2005	USA, Fin, Swe, Can	Two of four studies found an association between acute use of alcohol and fall risk. Modest evidence of a dose–response relationship with acute alcohol use was observed. Three of six studies found an association between usual alcohol use and increased fall risk, but the remaining studies did not.	Authors note that confounding was not adequately considered in a number of studies.

Key

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[b] Studies noted by authors to have a stronger capacity for causal inference.

3.2 Summary of data from Mendelian meta-analyses and pooled data analyses

Table 8. Summary of risk estimates: Mendelian randomisation approach

Study details	N studies	Study design		Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)					
		Co	Ca					Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Dose-response analysis	Subgroup analyses
Lewis & Davey Smith, 2005 Oesophageal cancer	7	-	7	1997-2002	Jpn, Tai, Tha	905	NA	 ALDH2*2*2 vs. *1*1 ALDH2*1*2 vs. *1*1 Overall Non-drinkers Heavy drinkers	 5 4 3 4	*Odds ratio* 0.36 (0.16–0.80) *Odds ratio* 3.19 (1.86–5.47) 1.31 (0.70–2.47) 7.07 (3.67–13.6)	 0.0% (0.71) 81.3% (<0.001) 0.0% (0.84) 66.7% (0.03)	NA	No evidence that effect estimates were related to study size.
Chen et al., 2008b Blood pressure	10	-	-	1994-2005	Jpn, UK	NR	NA	Hypertension ALDH2*1*1 vs. *2*2 ALDH2*1*2 vs. *2*2 Diastolic BP ALDH2 *1*1 vs. *2*2 ALDH2*1*2 vs. *2*2 Alcohol intake (per g/d) Systolic BP ALDH2*1*1 vs. *2*2 ALDH2*1*2 vs. *2*2 Alcohol intake (per g/d)	 3 3 5 5 3 5 5 3	*Odds ratio* 2.42 (1.66–3.55) 1.72 (1.17–2.52) *Mean diff mmHg* 3.95 (2.66–5.24) 1.58 (0.29–2.87) 0.16 (0.11–0.21) *Mean diff mmHg* 7.44 (5.39–9.46) 4.24 (2.18–6.31) 0.24 (0.16–0.32)	 0.0% (0.48) 0.0% (0.70) 0.0% (0.49) 0.0% (0.72) 0.0% (0.97) 18.0% (0.30) 12.1% (0.34) 0.0% (0.44)	NA	Some evidence that effect sizes were greater in smaller studies in meta-analysis of hypertension and in the analysis of male diastolic BP differences between ALDH2 genotypes.
Wang et al., 2011 Colorectal neoplasia	7	-	7	1999-2009	Jpn, Chn	2,392	NA	 ALDH2*1*1 vs. *2*2 ALDH2*1*2 vs. *2*2	 6 6	*Odds ratio* 1.31 (1.01–1.70) 1.13 (0.86–1.48)	 42.7% (0.12) 0.0% (0.46)		Sensitivity analysis showed similar results to overall analysis: *1*1 vs. *2*2 = 1.46 (1.09–1.97); *1*2 vs. *2*2 = 1.25 (0.92–1.69).

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Table 9. Summary of pooled risk estimates: Injury

Study details	N sites	Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)				
						Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Sensitivity analyses
Cherpitel et al., 2003a ERCAAP	31 (15 studies)	1984-2001	USA, Mex, Can, Aus, Spa, Ita, Arg	NR	-	5+ monthly drinking Positive BAC Self-report	 13 14	 4.27 (3.52–5.17) 3.89 (3.45–4.39)	 (0.004) (0.000)	Among non-heavy drinkers, frequent drinkers were more likely to have an alcohol-related injury than infrequent drinkers (OR 5.93; 3.70–9.50). Frequent heavy drinkers (vs. frequent light but infrequent heavy) were significantly more likely to have an alcohol related injury (OR 2.24; 1.69–2.99).
Cherpitel et al., 2003b ERCAAP	24	1984-2002	USA, Mex, Can, Aus, Spa, Ita, Arg, Pol	NR	Negative BAC No drinking	Positive BAC Fixed effect Random effect Self-reported volume Fixed effect Random effect	 12 12 13 13	 1.13 (0.80–1.59) 1.00 (0.50–1.99) 1.58 (1.40–1.78) 1.80 (1.37–2.37)	 (0.02) - (0.00) -	Pooled OR was smaller for those who reported drinking less frequently than weekly compared with those who reported drinking at least weekly or more often. Pooled ORs for those never consuming 5+ drinks on at least one occasion in the last year was not significant, but it was significant for those reporting 5+ yearly drinking.
Cherpitel et al., 2003c ERCAAP	30	1984-1997	USA, Mex, Can, Aus, Spa, Ita	NR	Negative BAC No drinking	Positive BAC Fixed effect Random effect Self-reported drinking Fixed effect Random effect	 29 29 29 29	 1.65 (1.31–2.06) 1.67 (1.26–2.22) 1.65 (1.48–1.84) 1.55 (1.24–1.93)	 (0.125) - (p<0.001) -	Level I trauma centre status was predictive of larger values of self-report effect size on admission to the ER with an injury. In multivariate analyses, both trauma centre and legal intoxication level were significant predictors.
Borges et al., 2006 ERCAAP, WHO–ER	28	1984-2002	Arg, Aus, Bls, Bra, Can, Chn, Cze, Ind, Mex, Moz, Nzl, Pol, Spa, Swe, USA, Zaf	11,536	No drinking	Fixed effect Random effect	28 28	5.47 (5.18–5.78) 5.69 (4.04–8.00)	(<0.001)	Higher levels of detrimental consumption patterns were associated with an increased effect size; higher per capita consumption was associated with a lower effect size. Only detrimental drinking pattern remained statistically significant in a multivariate model.

Key

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Table 10. Summary of pooled risk estimates: Cancer sites

Study details	N studies	Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)				
						Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Subgroup analyses
Cho et al., 2004 Pooling Project of Prospective Studies of Diet and Cancer Colorectal cancer	8	1980-1998	NR	4,687	Non-drinkers	30 to <45 g/d Overall Men Women ≥45 g/d Overall Men Women	 - - - - - -	 1.16 (0.99–1.36) 1.11 (0.86–1.45) 1.19 (0.94–1.50) 1.41 (1.16–1.72) 1.41 (1.11–1.79) 1.41 (0.98–2.02)		In analyses by type of beverage, drinking beer or wine was significantly associated with elevated risk and drinking spirits had a non-significant positive association. The difference among the 3 types of beverage was not statistically significant.
Collaborative Group on Hormonal Factors in Breast Cancer, 2002 Breast cancer	65	1984-2001	USA, Can, Nld, UK, Aus, Dnk, Nzl, Svn, Ger, Ita, Fra, Grc, Int	58,515	Non-drinkers	 All studies Cohort Case-control / pop Case-control / hosp	 65 - - -	*Increase in RR / 10g* 7.1 (SE 0.8) 5.0 (SE 1.7) 7.4 (1.1) 7.3 (1.7)		Compared to women who drank no alcohol, women drinking 35-44 g/d, RR = 1.32 (SE 0.059, P<0.00001) and drinking ≥45 g/d, RR = 1.46 (SE 0.060, P<0.00001).
Freudenheim et al., 2005 Pooling Project of Prospective Studies of Diet and Cancer Lung cancer	5	1980-1996	NR	3,137	Non-drinkers	≥30 g/d Men Women	 4 5	 1.21 (0.91–1.61) 1.16 (0.94–1.43)	 (0.09) (0.35)	RRs recalculated after reassigning all never smokers as former smokers were similar to the original calculations.
Genkinger et al., 2006 Pooling Project of Prospective Studies of Diet and Cancer Ovarian cancer	10	1980-2004	NR	2,001	Non-drinkers	≥30 g/d	-	1.12 (0.86–1.44)	(0.50)	No association was observed for alcohol from different types of beverages and ovarian cancer risk.

Study details	N studies	Years	Countries[a]	N cases	Reference category	Pooled risk estimates (categorical analysis)				
						Group	N	Effect estimate (95% CI)	Heterogeneity I^2 (p value)	Subgroup analyses
Morton et al., 2005 InterLymph Non-Hodgkin lymphoma	9	1990-2004	USA, Swe, UK, Ita	6,492	Non-drinkers	All studies	9	0.83 (0.76–0.89)	(0.244)	Data from 4 studies showed that compared with non-drinkers, risk for current drinkers was lower than that for former drinkers. The association between alcohol consumption and risk did not vary by beverage type, or by the combination of beverages consumed.
Purdue et al., 2009 INHANCE Head and neck cancer	15	1984-2006	Ita, Fra, Swi, Eur, USA, Pri, Sam, Spa, Ire, Pol, Can, Aus, Cub, Ind, Sud	9,107	Never drinkers	Beer Spirits Wine	15 15 15	2.1 (1.6–2.7) 2.2 (1.4–3.4) 1.6 (1.0–2.6)	(0.13) (<0.01) (<0.01)	Observed similar associations among beer-only and spirits-only drinkers as main analyses. Among wine-only drinkers, increases in risk were observed only for higher consumption levels (>30 drinks/week). Differences in the magnitude of risk at the highest consumption level were observed between geographic regions.

Key

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Appendix 1: Example search strategy

Medline via Ovid

1. Meta-Analysis As Topic/
2. (meta analy*).ti,ab
3. metaanaly*.ti,ab
4. Meta-Analysis/
5. (systematic adj1 (review* or overview*)).ti,ab
6. exp Review Literature As Topic/
7. or/1-6
8. cochrane.ti,ab
9. embase.ti,ab
10. (psychlit OR psyclit).ti,ab
11. (psychinfo OR psycinfo).ti,ab
12. (cinahl OR cinhal).ti,ab
13. (science citation index).ti,ab
14. bids.ti,ab
15. cancerlit.ti,ab
16. or/8-15
17. (reference list*).ti,ab
18. bibliograph*.ti,ab
19. hand-search*.ti,ab
20. (relevant journals).ti,ab
21. (manual search*).ti,ab
22. or/17-21
23. (selection criteria).ti,ab
24. (data extraction).ti,ab
25. 23 or 24
26. Review/
27. 25 and 26
28. 7 or 16 or 22 or 27
29. exp Alcohol Drinking/
30. exp Alcoholic Beverages/
31. Alcohol-Related Disorders/
32. Alcoholism/
33. Alcoholic Intoxication/
34. (alcohol* adj2 (drink or drinks or beverage*)).ti,ab
35. ((alcohol or ethanol) adj1 (consumption or drinking or intake or abuse or

misuse)).ti,ab

36. ((harmful or hazardous or problem or risky or heavy or excessive or binge or light or moderate) adj1 drinking).ti,ab
37. (drinking behavio?r or beer or wine or spirits or absinthe or liquor*).ti,ab
38. or/29-37
39. 28 AND 38
40. 39 [Limit to: Humans and Publication Year 1995-Current]

Appendix 2. AMSTAR tool criteria

Reproduced from: Shea et al. (2007). Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology, 7, 10.

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable

5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix 3: References to screened systematic reviews

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Appendix 4: Results of inclusion criteria screening

Table 11. Summary of inclusion criteria screening

Key to table
Q1: Does the review address an appropriate and clearly-focused question that is relevant to one or more of the key review questions?
Q2: Does the review include the types of studies relevant to the key review questions?
Q3: Is the literature search sufficiently rigorous to identify all the relevant studies?
Q4: Is the study quality of included studies appropriately assessed and reported?
Q5: Is an adequate description of the analytical methodology used included, and are the methods used appropriate to the question?

#	Reference details	Disease/health problem area	Q1	Q2	Q3	Q4	Q5
1.	Anstey, K. J., Mack, H. A. & Cherbuin, N. (2009)	Mental and behavioural disorders	Yes	Yes	Yes	No	Yes
2.	Bagnardi, V., Blangiardo, M., La Vecchia, C. & Corrao, G. (2001)	Neoplasms	No	Yes	Yes	No	Yes
3.	Bagnardi, V., Rota, M., Botteri, E., Scotti, L., et al. (2011)	Neoplasms	Yes	Yes	No	No	Yes
4.	Bagnardi, V., Zatonski, W., Scotti, L., La, C., et al. (2008)	Diseases of the circulatory system	Yes	Yes	No	No	Yes
5.	Baliunas, D. O., Taylor, B. J., Irving, H., Roerecke, M., et al. (2009)	Endocrine, nutritional and metabolic diseases	Yes	Yes	Yes	No	Yes
6.	Baliunas, D., Rehm, J., Irving, H. & Shuper, P. (2010)	Infectious and parasitic diseases	Yes	Yes	Yes	No	Yes
7.	Bandera, E., Freudenheim, J. & Vena, J. (2001)	Neoplasms	Yes	Yes	Yes	No	No
8.	Bay, B. & Kesmodel, U. S. (2011)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	Yes	Yes
9.	Bellocco, R., Pasquali, E., Rota, M., Bagnardi, V., et al. (2012)	Neoplasms	Yes	Yes	Yes	Yes	Yes
10.	Berg, K. M., Kunins, H. V., Jackson, J. L., Nahvi, S., et al. (2008)	Diseases of the musculoskeletal system	Yes	Yes	Yes	Yes	Yes
11.	Burger, M., Bronstrup, A. & Pietrzik, K. (2004)	Other	No	No	No	Yes	No
12.	Carlsson, S., Hammar, N. & Grill, V. (2005)	Endocrine, nutritional and metabolic diseases	Yes	Yes	No	No	No
13.	Chao, C. (2007)	Neoplasms	Yes	Yes	No	No	Yes
14.	Chen, L., Gallicchio, L., Boyd-Lindsley, K., Tao, X., et al. (2008a)	Neoplasms	Yes	Yes	Yes	Yes	Yes
15.	Cheng, G. & Xie, L. (2011)	Neoplasms	Yes	Yes	No	No	Yes
16.	Cheng, J. Y. W., Ng, E. M. L., Chen, R. Y. L. & Ko, J. S. N. (2007)	Mental and behavioural disorders	Yes	No	Yes	Yes	Yes
17.	Chong, E. W.-T., Kreis, A. J., Wong, T. Y., Simpson, J. A., et al. (2008)	Diseases of the eye	Yes	Yes	Yes	Yes	Yes
18.	Cleophas, T. J. (1999)	Diseases of the circulatory system	Yes	Yes	No	No	Yes
19.	Cook, R. L. & Clark, D. B. (2005)	Infectious and parasitic diseases	Yes	No	No	No	No
20.	Corrao, G., Bagnardi, V., Zambon, A. & Arico, S. (1999)	Other	Yes	Yes	Yes	Yes	Yes
21.	Corrao, G., Bagnardi, V., Zambon, A. & La Vecchia, C. (2004)	Other	Yes	Yes	Yes	Yes	Yes
22.	Corrao, G., Bagnardi, V., Zambon, A. & Torchio, P. (1998)	Diseases of the digestive system	Yes	Yes	No	Yes	Yes
23.	Corrao, G., Rubbiati, L., Bagnardi, V., Zambon, A., et al. (2000)	Diseases of the circulatory system	Yes	Yes	Yes	Yes	Yes
24.	Costanzo, S., Di Castelnuovo, A., Donati, M. B., Iacoviello, L., et al. (2011)	Diseases of the circulatory system	Yes	Yes	Yes	Yes	Yes
25.	Dennis, L. K. (2000)	Neoplasms	Yes	Yes	Yes	No	Yes
26.	Di Castelnuovo, A., Costanzo, S., Bagnardi, V., Donati, M. B., et al. (2006)	All-cause mortality	Yes	Yes	No	No	Yes
27.	Di Castelnuovo, A., Rotondo, S., Iacoviello, L., Donati, M. B., et al. (2002)	Diseases of the circulatory system	Yes	Yes	No	No	Yes
28.	Ellison, R., Zhang, Y., Mclennan, C. & Rothman, K. (2001)	Neoplasms	Yes	Yes	No	No	Yes
29.	Fedirko, V., Tramacere, I., Bagnardi, V., Rota, M., et al. (2011)	Neoplasms	Yes	Yes	No	Yes	Yes
30.	Feigin, V. L., Rinkel, G. J. E., Lawes, C. M. M., Algra, A., et al. (2005)	Diseases of the circulatory system	Yes	Yes	No	No	Yes

#	Reference details	Disease/health problem area	Q1	Q2	Q3	Q4	Q5
31.	Foran, H. M. & O'Leary, K. D. (2008)	External causes of morbidity and mortality	Yes	No	Yes	No	Yes
32.	Friberg, E., Orsini, N., Mantzoros, C. S. & Wolk, A. (2010)	Neoplasms	No	Yes	Yes	No	Yes
33.	Henderson, J., Gray, R. & Brocklehurst, P. (2007a)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	Yes	Yes
34.	Henderson, J., Kesmodel, U. & Gray, R. (2007)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	No*	Yes
35.	Holman, C. D., English, D. R., Milne, E. & Winter, M. G. (1996)	All-cause mortality	Yes	Yes	No	Yes	No
36.	Howard, A. A., Arnsten, J. H. & Gourevitch, M. N. (2004)	Endocrine, nutritional and metabolic diseases	Yes	Yes	No	Yes	Yes
37.	Irving, H. M., Samokhvalov, A. V. & Rehm, J. (2012)	Diseases of the digestive system	Yes	Yes	Yes	No	Yes
38.	Islami, F., Fedirko, V., Tramacere, I., Bagnardi, V., et al. (2011)	Neoplasms	Yes	Yes	No	No	Yes
39.	Islami, F., Tramacere, I., Rota, M., Bagnardi, V., et al. (2010)	Neoplasms	Yes	Yes	No	No	Yes
40.	Kan, H. P., Huang, Y. Q., Tan, Y. F. & Zhou, J. (2011)	Neoplasms	Yes	Yes	Yes	No	Yes
41.	Key, J., Hodgson, S., Omar, R. Z., Jensen, T. K., et al. (2006)	Neoplasms	Yes	Yes	Yes	Yes	Yes
42.	Kim, H. S., Kim, J. W., Shouten, L. J., Larsson, S. C., et al. (2010)	Neoplasms	Yes	Yes	Yes	No	Yes
43.	Kodama, S., Saito, K., Tanaka, S., Horikawa, C., et al. (2011)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
44.	Kool, B., Ameratunga, S. & Jackson, R. (2009)	External causes of morbidity and mortality	Yes	Yes	Yes	Yes	No
45.	Koppes, L. L. J., Bouter, L. M., Dekker, J. M., Heine, R. J., et al. (2005)	Endocrine, nutritional and metabolic diseases	Yes	Yes	No	No	Yes
46.	Koppes, L. L. J., Dekker, J. M., Hendricks, H. F. J., Bouter, L. M., et al. (2006)	Diseases of the circulatory system	Yes	Yes	No	No	No
47.	Korte, J. E., Brennan, P., Henley, S. J. & Boffetta, P. (2002)	Neoplasms	Yes	Yes	No	No	Yes
48.	Latino-Martel, P., Chan, D. S., Druesne-Pecollo, N., Barrandon, E., et al. (2010)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	No	No	Yes
49.	Lönnroth, K., Williams, B., Stadlin, S., Jaramillo, E., et al. (2008)	Infectious and parasitic diseases	Yes	Yes	No	No	Yes
50.	Mao, Q., Lin, Y., Zheng, X., Qin, J., et al. (2010)	Neoplasms	Yes	Yes	Yes	No	Yes
51.	Mazzaglia, G., Britton, R., Altmann, D. R. & Chenet, L. (2001)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
52.	McCambridge, J., McAlaney, J. & Rowe, R. (2011)	Other	Yes	Yes	Yes	Yes	Yes
53.	McFadden, C. B., Brensinger, C. M., Berlin, J. A. & Townsend, R. R. (2005)	Diseases of the circulatory system	Yes	Yes	No	No	Yes
54.	Middleton Fillmore, K., Chikritzhs, T., Stockwell, T., Bostrom, A., et al. (2009)	Neoplasms	Yes	Yes	No	No	Yes
55.	Moskal, A., Norat, T., Ferrari, P. & Riboli, E. (2007)	Neoplasms	Yes	Yes	No	No	Yes
56.	Neafsey, E. J. & Collins, M. A. (2011)	Mental and behavioural disorders	Yes	Yes	No	No	Yes
57.	Odendaal, H. J., Steyn, D. W., Elliott, A. & Burd, L. (2009)	Pregnancy and conditions originating in the perinatal period	No	Yes	No	No	No
58.	Padilla, H., Michael, J. & Djousse, L. (2010)	Diseases of the circulatory system	Yes	Yes	No	No	No
59.	Parsons, J. K. & Im, R. (2009)	Diseases of the genitourinary system	Yes	Yes	Yes	No	Yes
60.	Patra, J., Bakker, R., Irving, H., Jaddoe, V. W. V., et al. (2011)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	Yes	Yes
61.	Patra, J., Taylor, B., Irving, H., Roerecke, M., et al. (2010)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
62.	Pelucchi, C., Galeone, C., Tramacere, I., Bagnardi, V., et al. (2012)	Neoplasms	Yes	Yes	No	No	Yes
63.	Peters, R., Peters, J., Warner, J., Beckett, N., et al. (2008)	Mental and behavioural disorders	Yes	Yes	Yes	Yes	No
64.	Polygenis, D., Wharton, S., Malmberg, C., Sherman, N., et al. (1998)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	Yes	Yes
65.	Rehm, J., Samokhvalov, A. V., Neuman, M. G., Room, R., et al. (2009)	Infectious and parasitic diseases	Yes	Yes	Yes	No*	Yes
66.	Rehm, J., Taylor, B., Mohapatra, S., Irving, H., et al. (2010b)	Diseases of the digestive system	Yes	Yes	Yes	No	Yes
67.	Reid, M. C., Boutros, N. N., O'Connor, P. G., Cadariu, A., et al. (2002)	Other	Yes	Yes	No	Yes	No
68.	Reynolds, K., Lewis, B., Nolen, J., Kinney, G., et al. (2003).	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
69.	Rimm, E. B., Klatsky, A., Grobbee, D. & Stampfer, M. J. (1996)	Diseases of the circulatory system	No	Yes	No	No	No
70.	Roerecke, M. & Rehm, J. (2010)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
71.	Roerecke, M. & Rehm, J. (2011)	Diseases of the circulatory system	Yes	Yes	Yes	Yes	Yes
72.	Roerecke, M. & Rehm, J. (2012)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
73.	Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., et al. (2011)	Diseases of the circulatory system	Yes	Yes	Yes	Yes	Yes

#	Reference details	Disease/health problem area	Q1	Q2	Q3	Q4	Q5
74.	Rota, M., Bellocco, R., Scotti, L., Tramacere, I., et al. (2010)	Neoplasms	No	Yes	No	No	Yes
75.	Rota, M., Pasquali, E., Scotti, L., Pelucchi, C., et al. (2012a)	Neoplasms	Yes	Yes	No	No	Yes
76.	Rota, M., Scotti, L., Turati, F., Tramacere, I., et al. (2012b)	Neoplasms	Yes	Yes	No	No	Yes
77.	Samokhvalov, A. V., Irving, H. M. & Rehm, J. (2010b)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
78.	Samokhvalov, A. V., Irving, H. M. & Rehm, J. (2010c)	Diseases of the respiratory system	Yes	Yes	Yes	No	Yes
79.	Samokhvalov, A. V., Irving, H., Mohapatra, S. & Rehm, J. (2010a)	Diseases of the nervous system	Yes	Yes	Yes	No	Yes
80.	Shuper P. A., Neuman M., Kanteres F., Baliunas D., Joharchi N., Rehm J. (2010)	Infectious and parasitic diseases	No	No	No	No	No
81.	Smith, G. S., Branas, C. C. & Miller, T. R. (1999)	External causes of morbidity and mortality	Yes	Yes	Yes	No	No
82.	Song, D. Y., Song, S., Song, Y. & Lee, J. E. (2012)	Neoplasms	Yes	Yes	Yes	Yes	Yes
83.	Sun, Q., Xu, L., Zhou, B., Wang, Y., et al. (2011)	Neoplasms	Yes	Yes	Yes	No	Yes
84.	Suzuki, R., Orsini, N., MigNone, L., Saji, S., et al. (2008)	Neoplasms	Yes	Yes	No	No	Yes
85.	Taylor, B. & Rehm, J. (2012)	External causes of morbidity and mortality	Yes	Yes	Yes	No	Yes
86.	Taylor, B., Irving, H. M., Baliunas, D., Roerecke, M., et al. (2009)	Diseases of the circulatory system	Yes	Yes	Yes	No	Yes
87.	Taylor, B., Irving, H. M., Kanteres, F., Room, R., et al. (2010)	External causes of morbidity and mortality	Yes	Yes	Yes	No	Yes
88.	Testa, M., Quigley, B. M. & Eiden, R. D. (2003)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	No	Yes
89.	Teunissen, L. L., Rinkel, G. J. E., Algra, A. & Van Gijn, J. (1996)	Diseases of the circulatory system	Yes	Yes	No	No	No
90.	Tramacere, I., Negri, E., Bagnardi, V., Garavello, W., et al. (2010a)	Neoplasms	Yes	Yes	No	No	Yes
91.	Tramacere, I., Negri, E., Pelucchi, C., Bagnardi, V., et al. (2012a)	Neoplasms	Yes	Yes	No	No	Yes
92.	Tramacere, I., Pelucchi, C., Bagnardi, V., Rota, M., et al. (2012)	Neoplasms	Yes	Yes	No	No	Yes
93.	Tramacere, I., Pelucchi, C., Bonifazi, M., Bagnardi, V., et al. (2012b)	Neoplasms	Yes	Yes	No	No	Yes
94.	Tramacere, I., Scotti, L., Jenab, M., Bagnardi, V., et al. (2010b)	Neoplasms	Yes	Yes	No	Yes	Yes
95.	Turati, F., Gallus, S., Tavani, A., Tramacere, I., et al. (2010)	Neoplasms	Yes	Yes	No	No	Yes
96.	Turati, F., Garavello, W., Tramacere, I., Bagnardi, V., et al. (2010)	Neoplasms	Yes	Yes	No	No	Yes
97.	Turati, F., Garavello, W., Tramacere, I., Pelucchi, C., et al. (2013)	Neoplasms	Yes	Yes	No	No	Yes
98.	Wang, J., Pan, H. F., Ye, D. Q., Su, H., et al. (2008)	Diseases of the musculoskeletal system	Yes	Yes	Yes	Yes	No
99.	Zeegers, M. P., Tan, F. E., Verhagen, A. P., Weijenberg, M. P., et al. (1999)	Neoplasms	Yes	Yes	Yes	No	Yes
100.	Zeisser, C., Stockwell, T. R., Chikritzhs, T., Cherpitel, C., et al. (2013)	External causes of morbidity and mortality	Yes	Yes	Yes	No	Yes
101.	Zeka, A., Gore, R. & Kriebel, D. (2003)	Neoplasms	Yes	No	No	No	Yes
102.	Zhang, X., Zhang, Y. & Hu, Q. (2010)	Pregnancy and conditions originating in the perinatal period	Yes	Yes	Yes	No	No
103.	Zhu, K. J., Zhu, C. Y. & Fan, Y. M. (2012)	Diseases of the skin and subcutaneous tissue	Yes	Yes	No	No	Yes

Appendix 5. Data extraction tables and AMSTAR assessment

Table 12. Summary of methods: Systematic reviews and meta-analyses

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Anstey et al., 2009	**Databases searched:** PubMed, PsycINFO, Cochrane Library, **Years searched**: Inception to June 2007 **Keywords/MESH terms**: e.g. alcohol*, drink*, drunk*, cognit*, intell*, IQ, memory **Other strategies**: Reference lists of retrieved articles were screened **Limits**: English language	**Population(s):** NR **Exposure:** NR **Outcome(s):** Minimum 1-year follow-up, had to include dementia or cognitive decline. Studies needed to have (i) screened for dementia at baseline or adjusted for cognitive function; or (ii) measured cognition at baseline and follow-up and either dementia assessment at baseline (excluding participants with cognitive impairment or dementia) or adjusted for incident dementia and/or baseline cognition performance **Study design(s):** NR. Experimental and clinical studies were excluded **Process for selection:** Retrieved articles examined by at least two authors	**Data extraction variables**: Study design (sample source, number of participants, observation period), sample characteristics (percentage female, average age, years of education), measurement of alcohol (amount and type of alcohol consumed, history of past consumption, frequency of consumption), measurement of dementia or cognition, unadjusted and adjusted estimates of association with 95% confidence intervals and covariates. **Process for data extraction**: Double checked by a second reviewer who was blinded to the title, authors, publication date, and journal name of the article **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; fixed effects unless heterogeneity detected **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared tests **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** NR	5
Bagnardi et al., 2001	**Databases searched:** Medline, Current Contents, EMBASE, CAB Abstracts, Core Biomedical Collection **Years searched**: 1996–2000 **Keywords/MESH terms**: NR **Other strategies**: Screened references of retrieved studies, hand search of relevant journals, compared search results with other general reviews and meta-analyses. **Limits**: NR	**Population(s):** NR **Exposure:** NR **Outcome(s):** Expressed as relative risk or odds ratio **Study design(s):** Case-control or cohort study **Process for selection:** Two reviewers independently reviewed each article	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: NR **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** Based on methods proposed by Greenland and Longnecker.	2

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Bagnardi et al., 2011	**Databases searched:** Medline **Years searched**: 1960 to Jan 2010 **Keywords/MESH terms**: Ethanol, alcohol drinking, alcohol, alcoholic beverages, lung cancer, lung neoplasm **Other strategies**: Reference lists of retrieved articles and of reviews and meta-analyses published on the issue were screened **Limits**: English language	**Population(s):** Never smokers **Exposure:** Alcohol consumption **Outcome(s):** Lung cancer; risk estimates and CIs or calculable **Study design(s):** Case–control or cohort **Process for selection:** Three investigators independently determined the eligibility of each article for inclusion	**Data extraction variables**: Study design, country, gender, categories of alcohol intake considered, RR estimates and 95% CIs, adjustment variables and the number of cases and controls or the number of events and subjects at risk for the reported exposure levels **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistics **Assessment of publication bias**: Egger's test **Sensitivity analyses**: Influence analysis used (i.e. one study omitted at a time from the pooled analysis); compared the summary effect estimates for subgroups stratified on study or quality characteristics e.g. study design (cohort or case–control), geographic area, definition of 'never smokers', gender and adjustment for potential confounders. **Dose-response analyses:** Based on methods proposed by Greenland and Longnecker.	4
Baliunas et al., 2009	**Databases searched:** Medline, CINAHL, EMBASE, CAB Abstracts, WHOLIS, SIGLE, ETOH, Web of Science, AIM database. **Years searched**: Jan 1980 to Jan 2008 **Keywords/MESH terms**: Alcohol or ethanol, diabetes, case-control or cohort or prospective, and risk **Other strategies**: References of reviewed articles and relevant reviews screened. **Limits**: None	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Morbidity or mortality due to diabetes **Study design(s):** Cohort and case-control **Process for selection:** One researcher; limited duplication by a second researcher	**Data extraction variables**: Descriptors of study design, measure of association (hazard ratios, odds ratios, relative risks) **Process for data extraction**: One researcher; limited duplication by a second researcher **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q test, I^2 statistic **Assessment of publication bias**: Funnel plots; Egger and Begg tests **Sensitivity analyses**: Model variation by self-reported outcome for diabetes; analysis repeated using most adjusted estimates available. **Dose-response analyses:** Meta-regression using linear, first-order, and second order fractional polynomial regression of inverse variance–weighted data; Chi-squared distribution to determine best fit.	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Baliunas et al., 2010	**Databases searched:** Medline, PubMed, CINAHL, EMBASE **Years searched**: Inception to May 2008 **Keywords/MESH terms**: alcohol, ethanol, incidence, incident, risk, seroincidence, seroconvert*, HIV*, human immunodeficiency virus, STI, STIs, sexually transmitted infection*, STD, STD, sexually transmitted disease* **Other strategies**: None **Limits**: No language restrictions	**Population(s):** NR **Exposure:** Average consumption, binge consumption, and consumption prior to, or at the time of, sex **Outcome(s):** NR **Study design(s):** NR **Process for selection:** NR	**Data extraction variables**: Study design, measures of association, **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q-statistic and I^2 statistic **Assessment of publication bias**: Egger and Begg tests **Sensitivity analyses**: Stratified by sex, compared developed and developing countries, MSM vs. samples of other men. **Dose-response analyses:** NA	2.5
Bay & Kesmodel, 2011	**Databases searched:** Medline, Embase, Web of Science, Scopus and The Cochrane Library **Years searched**: NR; undertaken Feb 2010 **Keywords/MESH terms**: alcohol, alcohol drinking, alcohol-related disorders, pregnancy, motor skills, motor skills disorders, and child development **Other strategies**: Review of the reference lists of included papers **Limits**: English language	**Population(s):** NR **Exposure:** Categorized levels or continuous measures of average alcohol consumption or binge drinking and/or children with a diagnosis of FAS, children with reported maternal alcohol consumption in pregnancy and specialist-confirmed alcohol traits, and/or children of mothers with diagnosed alcoholism **Outcome(s):** Evaluation and scoring of children's motor function using standardised or validated test **Study design(s):** Cohort and case-control studies **Process for selection:** Reviewed independently by two authors	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: Newcastle–Ottawa Scale **Process for quality assessment**: NR	**How were studies combined**: Narrative synthesis **Measure of effect:** NA **Assessment of heterogeneity**: NA **Assessment of publication bias**: NA **Sensitivity analyses**: NA **Dose-response analyses:** NA	3

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Bellocco et al., 2012	**Databases searched:** Medline, EMBASE **Years searched**: 1966 to Nov 2010 **Keywords/MESH terms**: Alcohol drinking, kidney, renal cell carcinoma, cancer, neoplasm **Other strategies**: NR **Limits**: English language	**Population(s):** NR **Exposure:** At least three levels of alcohol consumption **Outcome(s):** Renal cell carcinoma; risk estimates and SE/CIs or calculable **Study design(s):** Cohort and case-control **Process for selection:** Three authors independently selected articles.	**Data extraction variables**: Study design, country, gender, categories of alcohol consumption, RR estimates and CIs, adjustment variables, and the number of cases and controls or number of events and cohort size. **Process for data extraction**: NR **Details of QA tool/checklist**: Quality score assigned based on the Newcastle and Ottawa scale **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared and I^2 statistic **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** Used a random effects meta-regression model in a nonlinear dose–response relationship framework to provide the best-fitting two-term fractional-polynomial model	6
Berg et al., 2008	**Databases searched:** MEDLINE, Cochrane Central Register of Controlled Trials, Current Contents, PsycINFO **Years searched**: NR; undertaken May 2007 **Keywords/MESH terms**: Alcohol, alcoholic, alcoholism, beer, wine, liquor, osteoporosis, osteopenia, bone mineral density, BMD, bone resorption (full details in article) **Other strategies**: Searched references of included studies and pertinent reviews **Limits**: English language	**Population(s):** Adults both exposed and not exposed to alcohol **Exposure:** **Outcome(s):** Osteoporotic fracture rate, bone density, bone response to oestrogen **Study design(s):** Experimental, cohort and case-control studies **Process for selection:** Two reviewers independently assessed each reference	**Data extraction variables**: Association between alcohol consumption and the outcome, adjustment for potential confounders. **Process for data extraction**: Two authors extracted data **Details of QA tool/checklist**: Based on internal validity criteria of the US Preventive Services Task Force **Process for quality assessment**: Number of reviewers NR; reports that differences were discussed until agreement reached.	**How were studies combined**: Meta-analysis (hip fracture); random effects **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistics **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** NA	5
Chen et al., 2008a	**Databases searched:** PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature Database System **Years searched**: Inception to Apr 2006 **Keywords/MESH terms**: **Other strategies**: Screened references in 1997 World Cancer Research Fund report, articles selected for extraction, and relevant review articles or meta-analyses **Limits**: None	**Population(s):** NR **Exposure:** Total alcohol, beer, wine, spirits, or any alcoholic beverages **Outcome(s):** Nasopharyngeal carcinoma **Study design(s):** NR; case reports and case series excluded **Process for selection:** Evaluated independently by two reviewers	**Data extraction variables**: Not fully described **Process for data extraction**: Extracted from the eligible articles by two reviewers using an electronic abstraction database **Details of QA tool/checklist**: Evaluated using a modification of the criteria used by Longnecker et al. **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistic **Assessment of publication bias**: Funnel plots **Sensitivity analyses**: Each study was excluded from the meta-analysis in turn **Dose-response analyses:** Conducted with models that tested for both linear and quadratic trends.	6.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Chong et al., 2008	**Databases searched:** PubMed, Web of Science, EMBASE, Medline, Cochrane Library, abstracts from the Association for Research in Vision and Ophthalmology, and National Institutes Of Health Clinical Trial Databases **Years searched**: Inception to Jun 2007 **Keywords/MESH terms**: alcohol, wine, beer, liquor, age-related macular degeneration, age-related maculopathy, macular degeneration, retinal degeneration, drusen, choroidal neovascularization, geographic atrophy **Other strategies**: References screened in pertinent articles and books **Limits**: No limits placed on the year or language of publication.	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Clear definition of age-related macular degeneration; estimates of odds ratios (ORs), relative risks, or the primary data to calculate. **Study design(s):** Prospective cohort studies; follow-up of at least one year; appropriate statistical techniques to adjust for key potential confounders (particularly age and smoking) **Process for selection:** Undertaken independently by two reviewers	**Data extraction variables**: NR **Process for data extraction**: Undertaken independently by two reviewers **Details of QA tool/checklist**: Downs & Black instrument; three ratings: A = high quality; B = moderate quality; C = low quality. **Process for quality assessment**: Undertaken independently by two reviewers	**How were studies combined**: Meta-analysis **Measure of effect:** Odds ratio **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Visual inspection of funnel plot **Sensitivity analyses**: Exclude volunteer-based studies and studies with the highest alcohol consumption category including consumption < 30 g/day **Dose-response analyses:** Unable to determine	7.5
Corrao et al., 2004	**Databases searched:** MEDLINE, Current Contents, EMBASE, CAB Abstracts, and Core Biomedical Collection **Years searched**: 1966-1998 **Keywords/MESH terms**: Alcohol consumption, relative risk, malignant neoplasms (oral cavity and pharynx, oesophagus, colon, rectum, liver, larynx, and breast), essential hypertension, coronary heart disease, haemorrhagic stroke, ischemic stroke, gastroduodenal ulcer, liver cirrhosis, chronic pancreatitis, injuries and violence. **Other strategies**: Screened reference lists of retrieved articles, hand search of relevant epidemiology and medicine journals, compared search with that of general reviews and meta-analyses published on this issue. **Limits**: NR	**Population(s):** NR **Exposure:** At least three levels of alcohol consumption **Outcome(s):** Odds ratio or relative risk **Study design(s):** Cohort and case-control **Process for selection:** Two researchers independently determined the eligibility of each paper. NB: Criteria for selection in the final analysis were: high quality score; reporting estimates adjusted for the main risk; or performed with a prospective cohort design.	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: Questions related to the study design (9 items), data collection methods for alcohol consumption (4 questions), and data analysis (2 items). **Process for quality assessment**: Two researchers independently scored the quality of the studies. Discrepancies resolved by discussion.	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q-statistic. **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** Four step procedure: (i) weighed least squares regression models fitted by prepooling the results of all included studies; (ii) meta-regression models fitted; (iii) pooled RR and corresponding 95% CIs were derived from the parameters of the meta-regression models; (iv) the consistency of the model based RR was evaluated with reference studies reporting relative risks for light consumption (≤25 g/day).	6

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Costanzo et al., 2011	**Databases searched:** PubMed, EMBASE **Years searched**: NR; undertaken Mar 2011 **Keywords/MESH terms**: alcohol, wine, beer, liquor, spirits, cardiovascular disease mortality, morbidity, survival, and death **Other strategies**: Screened references of retrieved articles and reviews **Limits**: English language	**Population(s):** NR **Exposure:** Different categories of alcohol exposure **Outcome(s):** Vascular mortality (cardiovascular disease, coronary heart disease and ischemic heart disease), non-fatal vascular events (acute myocardial infarction, stroke and coronary heart disease) **Study design(s):** NR **Process for selection:** Two authors independently reviewed articles	**Data extraction variables**: Alcohol intake (g/day) assigned as the midpoint of the reported ranges; frequency counts, adjusted RR, and 95% CI; covariates describing the characteristics of the study. **Process for data extraction**: NR **Details of QA tool/checklist**: Newcastle-Ottawa Scale; a second quality scale considered the assessment of alcohol drinking **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: NR **Assessment of publication bias**: Inspection of funnel plots; Egger test **Sensitivity analyses**: Tested the inclusion of interaction terms between the covariates (design of study, country setting, duration of follow-up) and alcohol intake (amount) **Dose-response analyses:** Models to be fitted were selected from among fractional polynomial curves of the second order. The best fit was defined as that with the highest likelihood.	7
Di Castelnuovo et al., 2006	**Databases searched:** PubMed **Years searched**: Inception to Dec 2005 **Keywords/MESH terms**: Alcohol, beer, wine, spirits, mortality, death **Other strategies**: Screened reference lists of retrieved studies. **Limits**: None	**Population(s):** NR **Exposure:** NR **Outcome(s):** All-cause mortality **Study design(s):** NR **Process for selection:** NR	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: **Assessment of publication bias**: **Sensitivity analyses**: **Dose-response analyses:** Models to be fitted were selected from among fractional polynomial curves of the second order. Best fitting curve defined as that with the highest likelihood; based on random effects model.	3

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Fedirko et al., 2011	**Databases searched:** PubMed **Years searched**: Inception to May 2010 **Keywords/MESH terms**: Alcohol, ethanol, alcoholic beverages, colorectal neoplasms **Other strategies**: Reference lists of the identified articles and previous literature reviews and meta-analyses were screened. **Limits**: English language	**Population(s):** NA **Exposure:** Total alcohol intake; at least three categories of consumption **Outcome(s):** Colorectal cancer incidence or mortality; risk reported as OR/RR **Study design(s):** Case-control or cohort **Process for selection:** NR	**Data extraction variables**: Study design, country, number of patients, duration of follow-up, type of controls, sex, variables adjusted for in the analysis, risk estimates for categories of alcohol consumption (and 95% CIs), the number of cases and non-cases or (person-years) for each level of alcohol consumption **Process for data extraction**: NR **Details of QA tool/checklist**: Predefined criteria (scoring 0-10) that addressed study design, assessment of alcohol drinking, and data analysis. **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** **Assessment of heterogeneity**: Chi-squared and I^2 statistic; subgroup analyses and meta-regression models conducted to investigate heterogeneity (further details not provided in methods) **Assessment of publication bias**: Egger and Begg-Mazumdar tests, trim and fill method, and contour enhanced funnel plots **Sensitivity analyses**: Assessed whether estimates were robust to the inclusion of studies (i) with a reference category for alcohol exposure different from non-drinkers, (ii) reporting estimates not adjusted for the main risk factors (age, sex, body fatness, smoking, and physical activity), and (iii) not reporting 95% CI for adjusted risk estimates. **Dose-response analyses:** Based on both linear and non-linear random effects models. Methods were adapted to account for correlation between reported risk estimates within the same study, heterogeneity between the studies, and a nonlinear dose–risk relation. The final dose–risk relation model was selected from tests of fractional polynomial random effects models and linear random effect models (defined as the one with the lowest Akaike's information criterion).	6

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Henderson et al., 2007a; 2007b	**Databases searched:** Medline, EMBASE, CINAHL, PsycINFO **Years searched**: Inception to 2005 **Keywords/MESH terms**: Full strategy reported **Other strategies**: NR **Limits**: Published between Jan 1970 and Jul 2005; English language; peer-reviewed articles	**Population(s):** **Exposure:** Average weekly alcohol consumption grouped into two or more categories; or measure of binge drinking reported separately from heavy drinking **Outcome(s):** Miscarriage, stillbirth, intrauterine growth restriction, preterm birth, low birth weight, small for gestational age at birth or birth defects including fetal alcohol syndrome or neurodevelopmental outcomes **Study design(s):** Case–control, cohort or cross-sectional studies **Process for selection:** Reviewed independently by two members of the research team	**Data extraction variables**: NR **Process for data extraction**: Each article was data extracted by a single reviewer and checked for accuracy by a second **Details of QA tool/checklist**: Newcastle–Ottawa Scale **Process for quality assessment**: NR	**How were studies combined**: Narrative synthesis **Measure of effect:** NA **Assessment of heterogeneity**: NA **Assessment of publication bias**: NA **Sensitivity analyses**: NA **Dose-response analyses:** NA	4
Irving et al., 2012	**Databases searched:** Medline, EMBASE, CINAHL, Web of Science, ETOH and AIM **Years searched**: Jan 1980 – Jan 2008 **Keywords/MESH terms**: Alcohol, alcohol consumption, alcohol intake, ethanol, heavy drinking, and pancreatitis **Other strategies**: Hand searched content pages of major epidemiological journals; screened reference lists of relevant and review articles **Limits**: Human studies, no language restrictions applied	**Population(s):** NR **Exposure:** Three or more quantitatively measured exposure categories of alcohol consumption **Outcome(s):** Pancreatitis morbidity and/or mortality; report hazard ratios, relative risks or odds ratios and their 95% confidence intervals (or information to compute them) **Study design(s):** Case-control or cohort study **Process for selection:** NR	**Data extraction variables**: Study details, year of publication, sample size, country, age, sex, endpoints, adjustments, study design, exposure and outcome measures, RRs of pancreatitis and corresponding 95% CIs for each category of alcohol consumption **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistics **Assessment of publication bias**: Visual inspection of Begg's funnel plot; Begg-Mazumdar and Egger tests **Sensitivity analyses**: **Dose-response analyses:** Methods proposed by Greenland and Longnecker; fitted first and second degree fractional polynomial models using a random effects model; best fitting model selected based on a closed-test comparison between fractional polynomial models	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Islami et al., 2010	**Databases searched:** PubMed **Years searched**: Inception to May 2010 **Keywords/MESH terms**: Alcohol, alcoholic beverage, ethanol, wine, beer, spirit, drinking, intake, consumption, drinking pattern, larynx, neoplasm, cancer, tumor, Laryngeal neoplasm **Other strategies**: Searched the bibliographies of relevant original and review articles, a recent systematic report, and IARC monograph reports **Limits**: NR	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Laryngeal cancer; ratio measure of effect and CIs **Study design(s):** Case-control or cohort **Process for selection:** NR	**Data extraction variables**: Design and country of studies, number and sex of participants, source of controls and duration of follow-up, variables for which study results were controlled, number of cases and non-cases for each alcohol consumption level, and RRs and corresponding 95% CIs for each category. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Begg and Mazumdar's test, Egger's test, funnel plots **Sensitivity analyses**: Selected only studies: (1) with population-based controls; (2) using exclusively non-drinkers as reference category; and (3) presenting RRs adjusted for main potential confounding factors (age, sex, and tobacco use). **Dose-response analyses:** Used a random-effects meta-regression model in a non-linear dose–risk relationship framework to provide the best-fitting two-term fractional–polynomial model.	4

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Islami et al., 2011	**Databases searched:** PubMed **Years searched**: Jan 1999 to Jun 2010 **Keywords/MESH terms**: Esophageal neoplasms, cohort, prospective, case-control, case control **Other strategies**: Reviewed bibliographies of relevant original and review articles and systematic reports; used a list of publications prepared for an earlier meta-analysis (articles published up to 2000) **Limits**: English language	**Population(s):** NR **Exposure:** Total alcohol intake **Outcome(s):** Oesophageal squamous cell carcinoma or all oesophageal cancer combined; risk estimates and CIs or calculable **Study design(s):** Case-control or cohort **Process for selection:** NR	**Data extraction variables**: Study design, study area and period, number of participants, sex, source of controls, variables controlled for, number of cases and non-cases, RR and CIs for each alcohol consumption level **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Begg's and Egger's tests **Sensitivity analyses**: Subgroup analyses including: (i) only prospective studies; (ii) studies with more precise estimates (i.e. those with SE <0.5 [light/moderate or <0.3 [heavy]); (iii) only population–based controls; (iv) oesophageal squamous cell carcinoma only; (v) geographic area; (vi) estimates adjusted for main potential confounding factors (age, sex and smoking); (vii) sex; (viii) excluding two studies that reported adjusted RRs without 95% CIs; (ix) excluding two studies with potential overlap with other studies; (x) studies with exclusively non-drinkers as the reference category; and (xi) mortality vs. incidence. **Dose-response analyses:**	3
Kan et al., 2011	**Databases searched:** Medline, EMBASE, the Cochrane Library **Years searched**: 1966-2010 **Keywords/MESH terms**: Alcohol, extrahepatic bile duct, cancer, biliary tract cancers, cholangiocarcinoma, gallbladder cancer, Vater's ampulla cancer **Other strategies**: References in abstracted articles and previous relevant reviews screened **Limits**: English language	**Population(s):** NR **Exposure:** NR **Outcome(s):** RR or equivalent **Study design(s):** Case–control or cohort **Process for selection:** NR	**Data extraction variables**: Authors, published year, country, age range, study design, participant number and adjusting variables **Process for data extraction**: Data abstracted independently by two reviewers **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Odds ratio **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Begg's and Egger's tests **Sensitivity analyses**: Excluded studies which potentially biased the results **Dose-response analyses:** NA	4

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Key et al., 2006	**Databases searched:** Medline, EMBASE, Pascal, Science Citation Index, Social Sciences Citation Index, Index to Scientific and Technical Proceedings, Biological Abstracts (BIOSIS), Biological Sciences, AIDS and Cancer Research Abstracts, Biology Digest, Conference Papers Index, Cochrane Library, NHS National Research Register (NRR), SIGLE, NTIS, TOXLINE **Years searched**: Jan 1966 to Dec 2003 **Keywords/MESH terms**: Breast, neoplasm, ethanol **Other strategies**: Screened reference lists of identified articles, citation searching, identification of grey literature, and searches of conference proceedings. **Limits**: None	**Population(s):** NR **Exposure:** NR **Outcome(s):** incident first primary breast cancer **Study design(s):** Case-control and cohort **Process for selection:** NR	**Data extraction variables**: NR **Process for data extraction**: Data abstracted independently by two reviewers **Details of QA tool/checklist**: Simple three-point scoring system used; 1 = studies with inadequate design; 2 = studies with acceptable design but insufficient control for confounding; 3 = studies with acceptable design and adequate control for confounding. **Process for quality assessment**: Studies scored independently by two reviewers	**How were studies combined**: Meta-analysis **Measure of effect:** Odds ratio **Assessment of heterogeneity**: Q statistic, meta-regression (data collected before or after disease onset, whether the controls were hospital or community based [case-control studies]; pre or postmenopausal; and nationality of the study population [USA or Can/Europe/other]) **Assessment of publication bias**: Funnel plots **Sensitivity analyses**: Assessed how differing quality criteria and control for confounding affected d the size of the risk estimate. **Dose-response analyses:** Used "pool-first" method then calculated dose-response slopes (among drinkers) for each study by use of log linear regression and a variable intercept; dose-response slopes were pooled using a random effects model.	6.5
Kodama et al., 2011	**Databases searched:** Medline, EMBASE **Years searched**: Inception to Dec 2009 **Keywords/MESH terms**: Alcohol drinking, alcohol related, disorders, alcoholism, alcoholic beverage, ethanol, arrhythmias, atrial fibrillation **Other strategies**: Screened reference lists from identified articles **Limits**: No language restrictions	**Population(s):** NR **Exposure:** Daily alcohol consumption **Outcome(s):** Identify atrial fibrillation separate from other arrhythmias; report (or allow calculation of) effect measures and corresponding 95% CIs **Study design(s):** Cohort or case-control study **Process for selection:** Independently reviewed by two authors	**Data extraction variables**: Study details, year of publication, geographic region, study design, selection of study population, participants' characteristics, characteristics of outcome, methods of assessment of alcohol consumption, methods for ascertainment of atrial fibrillation, category of alcohol intake, number of participants and cases, and study-specific controlled variables. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistics **Assessment of publication bias**: Visual inspection of a funnel plot; Begg and Egger tests; "trim and fill" procedure **Sensitivity analyses**: Meta-regression analyses used to assess the influence of study characteristics on study results. **Dose-response analyses:** Weighted, least-squared regression models used; also restricted cubic splines with knots at the 25th, 50th, and 75th centiles of the distribution of alcohol consumption.	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Kool et al., 2009	**Databases searched:** Medline, EMBASE, CINAHL, PsycINFO, and Scopus **Years searched**: 1983 to 2007 **Keywords/MESH terms**: Accidental falls, accidents, home, alcohol, ethyl, BAC, alcohol drinking. **Other strategies**: Reference lists of retrieved articles, proceedings of conferences, hand-searching journals, internet searches (policy and research websites) and contact with key researchers in the field. **Limits**: English language papers.	**Population(s):** Young and middle aged adults aged 25-60 years. Studies including subjects in residential care, work-related falls, or studies of injuries limited to a specific body region (e.g., hip fracture, traumatic brain injury, maxillofacial injuries) were excluded. **Exposure:** Acute or usual alcohol consumption (a defined period immediately prior to the event) **Outcome(s):** Magnitude of fall risk, self-reported falls (injurious and non injurious),ED visit or admission to hospital for a fall related injury, death as a result of a fall-related injury and fractures as a result of falls. **Study design(s):** Case control, cohort , case-crossover studies **Process for selection:** NR	**Data extraction variables**: Participants, comparison group, exposure, confounders considered, outcomes, results and study quality **Process for data extraction**: NR **Details of QA tool/checklist**: GATE LITE (a visual framework used to appraise epidemiological studies). **Process for quality assessment**: NR	**How were studies combined**: Narrative synthesis; meta-analysis was not attempted because of the heterogeneity of the eligible studies **Measure of effect:** NA **Assessment of heterogeneity**: Identified studies were heterogeneous in many respects and were not considered sufficiently robust to combine quantitatively. **Assessment of publication bias**: NA **Sensitivity analyses**: NA **Dose-response analyses:** NA	4.5
Latino-Martel et al., 2010	**Databases searched:** Pubmed **Years searched**: up to May 7 2009 **Keywords/MESH terms**: Leukaemia, alcohol drinking, alcoholic beverages, ethanol, acetaldehyde, risk, risk factor, risk assessment, food, pregnancy, maternal exposure, prenatal exposure delayed effects, maternal-fetal exchange, prenatal nutrition physiology, parents, fetal alcohol syndrome **Other strategies**: In-process publications were searched and the reference list of relevant articles and reviews. **Limits**: No language restrictions.	**Population(s):** Children aged 0-18 years **Exposure:** Maternal alcohol intake during pregnancy (compared with no alcohol intake) **Outcome(s):** Risk of childhood leukaemia **Study design(s):** Case control studies **Process for selection:** NR	**Data extraction variables**: Study design, first author, publication year, country, case recruitment period, number and characteristics of cases and controls, alcohol consumption assessment, participation rate of cases and controls, age of children, leukaemia type, control for confounding, and additional information **Process for data extraction**: Data extracted independently by two investigators using a standardised data collection form, and then compared **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Odds ratio **Assessment of heterogeneity**: Cochrane Q test and I^2 statistic. **Assessment of publication bias**: Funnel plots, Egger's test. **Sensitivity analyses**: Analyses conducted by type of leukaemia, age at diagnosis, alcoholic beverage, and pregnancy trimester if at least three studies available. **Dose-response analyses:** Dose-response meta-analyses used method proposed by Greenland and Longnecker. Dose-response slopes for an increment of one drink per week were estimated using the midpoint of each category of alcohol intake.	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Lönnroth et al., 2008	**Databases searched:** PubMed **Years searched**: NR **Keywords/MESH terms**: Alcohol, alcoholism, tuberculosis **Other strategies**: Private collection of scientific tuberculosis publications; screened a report of a systematic review of the association between smoking and tuberculosis; reference lists of all reviewed articles screened. **Limits**: NR	**Population(s):** NR **Exposure**: Amount of alcohol intake or a clinical diagnosis of an alcohol use disorder **Outcome(s):** Active tuberculosis **Study design(s):** Case-control and cohort studies **Process for selection:** NR	**Data extraction variables**: Setting, inclusion criteria of study subjects, definition of exposure and outcome, mechanisms for ascertainment of exposure and outcome, and confounders were controlled for. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment:** NR	**How were studies combined**: Meta-analysis **Measure of effect**: Adjusted odds ratio **Assessment of heterogeneity**: Q test, I^2 statistic **Assessment of publication bias**: Funnel plots **Sensitivity analyses**: Excluded three studies with highest standard errors. **Dose-response analyses:** NA	3.5
Mao et al., 2010	**Databases searched:** Medline, PubMed, Web of Science, and the Cochrane Library. **Years searched**: 1980-2009 **Keywords/MESH terms**: Alcohol, bladder cancer **Other strategies**: References of reviewed articles and previous reviews screened. **Limits**: English language	**Population(s):** NR **Exposure:** NR **Outcome(s):** Bladder cancer **Study design(s):** Case-control and cohort **Process for selection:** NR	**Data extraction variables**: Reference details, study design, sample size, anatomical size of the neoplasm, adjusted effect estimates, exposure assessment, adjusted covariates. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Odds ratio (relative risks were assumed to approximate to an odds ratio) **Assessment of heterogeneity**: Random effect model; Q test, I^2 statistic. Meta-regression used to explore influence of study design, geographical region, alcohol assessment, and publication year. **Assessment of publication bias**: Egger and Begg tests. **Sensitivity analyses**: Sex, study design, study location, smoking status and type of alcohol (beer, wine or spirits). **Dose-response analyses:** NR	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
McCambridge et al., 2011	**Databases searched:** Medline, Web of Knowledge, Global Health Archive, CINAHL, PsycInfo, EMBASE and Health Management Information Consortium **Years searched**: 1964 to 2008 **Keywords/MESH terms**: Adolescent, teen, young person, young people, young adult, alcohol, binge drinking, drinking culture, problem drinking, drinking problem, hazardous drinking, substance, adult, cohort, longitudinal, prospective, lifetime **Other strategies**: Citation searching; bibliographies of relevant studies checked and Science Citation Index used for citation searches. Three journals were hand searched: Addiction Abstracts; Addiction; and Journal of Studies on Alcohol and Drugs. Experts were contacted for further information. **Limits**: Only peer-reviewed published data were used	**Population(s):** Cohorts formed from general population sources. Specific populations including children of alcoholic parents, mental health patients and offenders were excluded **Exposure:** Alcohol consumption between ages 15 to 19 years. **Outcome(s):** Behavioural effects (and associated harm) at age 20 or greater. **Study design(s):** Cohort studies **Process for selection:** Undertaken independently by two reviewers; second reviewer was blinded to the outcome of the first.	**Data extraction variables**: Cohort type, age, sample size, follow up rate, adolescent behavioural variables, adult outcomes **Process for data extraction**: Duplicated by a second reviewer. **Details of QA tool/checklist**: Authors assessed likelihood of residual confounding and whether each study had at least one of the following characteristics: (1) follow-up rates of 80% or greater; or (2) sample sizes of 1,000 participants or more. **Process for quality assessment:** Two reviewers undertook assessment, disagreements were resolved by discussion.	**How were studies combined**: Narrative synthesis; meta-analysis was deemed inappropriate **Measure of effect:** NA **Assessment of heterogeneity**: NA **Assessment of publication bias**: NA **Sensitivity analyses**: NA **Dose-response analyses:** NA	3
Parsons et al., 2009	**Databases searched:** Medline, the Cochrane Library, Web of Science and abstracts from AUA annual meetings (2002-2008). **Years searched**: Up to Mar 2008 **Keywords/MESH terms**: Prostatic hyperplasia, lower urinary tract symptoms and alcohol **Other strategies**: Reviewed the references of retrieved articles. **Limits**: English language publications	**Population(s):** NR **Exposure:** Alcohol intake **Outcome(s):** Benign prostatic hyperplasia or lower urinary tract symptoms **Study design(s):** Case control or cohort study. **Process for selection:** If eligibility disagreement occurred, the senior investigator made final decision.	**Data extraction variables**: Study design, outcomes, adjusted effect estimates, categories/quantities of alcohol intake, and covariates in final adjusted models. Pooled analysis – total alcohol consumption, exposure levels. **Process for data extraction**: NR **Details of QA tool/checklist**: Did not use a formal score for quality assessment. **Process for quality assessment**: NA	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared test **Assessment of publication bias**: Egger's test, Begg-Mazumdar test. **Sensitivity analyses**: Repeated analyses after substituting different measures of intake and excluding studies that measured incident benign prostatic hyperplasia. **Dose-response analyses:** Not applicable	3.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Patra et al., 2010	**Databases searched:** Medline, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science **Years searched**: Jan 1980 to Jun 2009 **Keywords/MESH terms**: Alcohol, ethanol, stroke, cerebrovascular, intracranial embolism, thrombosis, case, cohort, ratio, risk, prospective, follow **Other strategies**: Bibliographies of key retrieved articles, relevant reviews and meta-analyses were hand searched. **Limits**: None	**Population(s):** NR **Exposure:** Three or more alcohol exposure groups **Outcome(s):**Medically confirmed ischemic or haemorrhagic stroke **Study design(s):** Cohort or case-control study **Process for selection:** NR	**Data extraction variables**: Study details, source of publication, country of origin, study design, characteristics of the study population, measures of outcome and exposure, duration of follow-up, confounding factors controlled for by matching or adjustment, and RR and corresponding 95% confidence intervals of stroke types, assessment of current or life time abstention, and level of alcohol consumption. RRs were abstracted by sex, subtype of stroke (ischemic or haemorrhagic), end point incidence (mortality, morbidity), and level of alcohol consumption. **Process for data extraction**: Five included and five excluded studies randomly chosen to be abstracted independently by a second reviewer. Where disagreements existed, both authors discussed until a consensus was reached. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane Q test, I^2 statistic. **Assessment of publication bias**: Visual inspection of Begg's funnel plot; Begg–Mazumdar test and the Egger's test **Sensitivity analyses**: Examined impact of each stroke type. **Dose-response analyses:** Conducted using linear and first- and second-order fractional polynomials to estimate a best fitting curve to the data. Best-fit curves or lines were assessed using standard goodness-of-fit statistics with an emphasis on reduced deviance (gain) compared with the quadratic model.	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Patra et al., 2011	**Databases searched:** Medline, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH and Web of Science **Years searched**: Jan 1980 to Jun 2009 **Keywords/MESH terms**: Alcohol, ethanol, light drinking, moderate drinking, birth weight, low birth weight, gestational age, small for gestational age, preterm, pregnancy outcome, pregnancy complication, prenatal, case, cohort, ratio, risk, prospective, follow **Other strategies**: Reference lists hand searched **Limits**: No language restrictions were applied.	**Population(s):** NR **Exposure:** Alcohol consumption before and during pregnancy **Outcome(s):** Medically confirmed low birth weight (<2500 g), preterm birth (<37 weeks) and small for gestational age (<10th percentile of gestational age-adjusted birth weights) **Study design(s):** Case control and cohort studies reporting incidence, hazard ratios, relative risks or odds ratios. **Process for selection:** Reviewed independently by two reviewers. Discrepancies were resolved in consultation with a third reviewer	**Data extraction variables**: Author details, publication year, source of publication, country of origin, study design, characteristics of the study population, measures of outcome and exposure, duration of follow-up , confounding factors controlled for by matching or adjustment, and the risk estimates (relative risk or odds ratios or hazard ratios) of birth outcomes studied, compared with abstainers, associated with alcohol consumption and the corresponding confidence intervals **Process for data extraction**: All data were independently extracted by means of a standardised protocol. Five included and five excluded studies randomly chosen to be abstracted independently by a second reviewer. Where disagreements existed, both authors discussed until a consensus was reached. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane Q test, I^2 statistic. **Assessment of publication bias**: Visual inspection of Begg's funnel plot; Begg–Mazumdar test and the Egger's test **Sensitivity analyses**: Examined type of study and compared risks of both pregnancy outcomes on pre-pregnancy (i.e. until pregnancy is known) and during pregnancy. **Dose-response analyses:** Conducted meta-regression using linear as well as first- and second-order fractional polynomial regression to estimate a best fitting curve to the data (assessed using decreased deviance compared with the reference model).	5
Pelucchi et al., 2012	**Databases searched:** PubMed **Years searched**: Inception to Oct 2010 **Keywords/MESH terms**: alcohol, ethanol, bladder, urinary tract, cancer, neoplasm, carcinoma, case-control, case-control studies, cohort, cohort studies, epidemiology **Other strategies**: Reference list of all papers of interest screened. **Limits**: NR	**Population(s):** NR **Exposure:** Considered at least three levels of alcohol consumption. **Outcome(s):** OR/RR estimates and corresponding CI (or information sufficient to calculate them) **Study design(s):** Case-control and cohort studies. **Process for selection:** Two authors assessed potentially relevant articles.	**Data extraction variables**: Study design, country, period of enrolment and/or follow-up, number of subjects (cases, controls or non-cases or cohort size), gender, covariates adjusted for in the analysis, risk estimates for categories of alcohol consumption, the number of cases and non-cases for each level of alcohol consumption considered. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared test. **Assessment of publication bias**: **Sensitivity analyses**: Excluded each study at a time from the meta-analysis **Dose-response analyses:** NA	4

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Peters et al., 2008	**Databases searched:** Medline, EMBASE, and PsycInfo **Years searched**: 1995 to Mar 2006. **Keywords/MESH terms**: Alcohol, wine, beer, dementia, vascular dementia, multi-infarct dementia, Alzheimer's disease, cognitive Impairment, cognitive decline **Other strategies**: None **Limits**: English language publications relating to humans. Authors report that all searches were limited to people aged 65 years and above.	**Population(s):** People aged 65 years and above **Exposure:** Alcohol consumption **Outcome(s):** Incident cognitive decline/dementia **Study design(s):** Case control studies **Process for selection:** Two reviewers appraised all studies independently; discrepancies in decisions were discussed.	**Data extraction variables**: NR **Process for data extraction**: Content was summarised in extraction tables independently by two reviewers. **Details of QA tool/checklist**: Assessed using 'standard' criteria assessing key factors (e.g. appropriate design, recruitment, analysis, and provision of suitable information relating to key aspects of the study). (Authors refer to Alberta Heritage Foundation for Medical Research 2004) **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: NR **Assessment of publication bias**: NR **Sensitivity analyses**: NR **Dose-response analyses:** Not applicable	4.5
Rehm et al., 2010	**Databases searched:** Medline, EMBASE, Web of Science, CINAHL, PsycInfo, ETOH and Google Scholar **Years searched**: Jan 1980 to Jan 2008 **Keywords/MESH terms**: Alcohol, alcohol consumption, alcohol intake, heavy drinking, liver diseases and liver cirrhosis **Other strategies** Reviewed content pages of major epidemiological journals and the searched reference lists **Limits**: None	**Population(s):** NR **Exposure:** Three or more categories of alcohol consumption **Outcome(s):** Clinically defined liver cirrhosis morbidity and/or mortality (defined as ICD codes: 581 in ICD7 and 571 in ICD8 and ICD9, and K70, K74 in ICD10). **Study design(s):** Case control or cohort study **Process for selection:** NR	**Data extraction variables**: Study details, sample size, country, region, ethnicity, age, sex, end-points, adjustments, design of the study baseline, methods of interview, time period of alcohol consumption, number of beverages, patterns of drinking, and RR with corresponding 95% CIs for each category of alcohol consumption. **Process for data extraction**: Independently extracted by two reviewers. Third reviewer extracted data from a random sample of 15 articles to assess inter-rater reliability. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane *Q*-test, I^2 statistic **Assessment of publication bias** Egger's test, Begg-Mazumdar test **Sensitivity analyses**: Sensitivity analyses were conducted to check if this procedure resulted in biased results compared with restricting the analyses to 'pure' categories, and excluding studies with 'mixed' categories. **Dose-response analyses:** Used the method proposed by Greenland *et al.* to back calculate and pool study-specific trend estimates.	6

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Roerecke & Rehm, 2010	**Databases searched:** Medline, EMBASE, Web of Science, ETOH, National Institute on Alcohol Abuse and Alcoholism and AIM. **Years searched**: Jan 1980 to Jul 2008 (updated to Dec 2008) **Keywords/MESH terms**: Alcohol, ethanol, heavy drinking occasion, heavy episodic drinking, binge drinking, alcoholic intoxication, problem drinking, hangover, irregular, pattern, inebriation, coronary heart disease, coronary artery disease, ischemic heart disease, ischaemic heart disease, myocardial infarction, sudden cardiac death, angina pectoris, coronary death, case cohort, ratio, risk, prospective, follow **Other strategies**: Screened references of retrieved articles **Limits**: No language restrictions were applied. Peer reviewed publications.	**Population(s):** NR **Exposure:** Heavy drinking episodes (≥60 g or ≥5 standard drinks per occasion) or intoxication **Outcome(s):** Ischaemic heart disease (defined according to standard WHO criteria) **Study design(s):** Cohort or case control studies reporting incidence, hazard ratios, relative risks, or odds ratios **Process for selection:** One reviewer assessed inclusion based on titles and abstracts; potentially eligible studies were screened jointly by two reviewers.	**Data extraction variables**: Study design, endpoint, exposure assessment, and adjustment for confounders. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane's Q-test, I^2 statistic **Assessment of publication bias**: Examined small study effects. **Sensitivity analyses**: Omitted each study separately from the meta-analyses **Dose-response analyses:** Potential dose-response relationship examined by including a dummy variable representing 9 or more drinks per irregular heavy drinking occasion on the within-study level.	4.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Roerecke & Rehm, 2012	**Databases searched:** Medline, EMBASE and Web of Science. **Years searched**: Jan 1980 to Apr 2010 **Keywords/MESH terms**: Alcohol drinking, alcoholic beverages, beverages, alcohol, drinking, intake, consumption, ethanol, drinking, intake, consumption, myocardial ischemia, myocardial infarct, coronary disease, heart diseases, coronary artery disease, coronary heart disease, angina, cardiac death, ischaemic heart disease, ischaemic heart disease, cardiac event, coronary event, cohort studies, epidemiologic studies, follow up studies, longitudinal studies, prospective studies, case control studies, retrospective studies, ratio, risk **Other strategies**: Reference lists screened for relevant studies. **Limits**: None	**Population(s):** NR **Exposure:** At least three categories of alcohol consumption among current drinkers; cover a reference period >2 weeks for average alcohol consumption at baseline; determined by at least a combination of usual frequency and usual volume or the number of drinks in the specified reference period. **Outcome(s):** Clinically defined ischaemic heart disease morbidity or mortality (defined as ICD codes: ICD-9: 410–414, ICD-10: I20–25) **Study design(s):** Cohort or case control studies **Process for selection:** One reviewer assessed inclusion based on titles and abstracts; potentially eligible studies were screened jointly by two reviewers.	**Data extraction variables**: Relative risk estimates and corresponding variances, number of cases and controls or people at risk for each reported category of average alcohol intake (if not directly reported, we estimated these based on standard formulas) study design, end-point, sex, country, age at baseline, length of follow-up, first year of baseline assessment and specific adjustment for covariates. We converted alcohol intake into g/day using the mid-points **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane's *Q* test, I^2 statistic **Assessment of publication bias**: 'Peter's regression-based test' **Sensitivity analyses**: Influence of single studies was examined by omitting studies one by one and re-estimating the pooled RR. **Dose-response analyses:** Used fractional polynomials to derive the best-fitting function using the 'pool first' approach. Goodness-of-fit statistics were used to choose the best-fitting model.	4.5
Rota et al., 2012a	**Databases searched:** Medline **Years searched**: Inception to Sep 2011 **Keywords/MESH terms**: Alcohol drinking, alcoholic beverages, ethanol, epithelial ovarian cancer, epithelial ovarian neoplasms **Other strategies**: Reference lists from relevant studies, reviews and meta-analysis screened. **Limits**: NR	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Epithelial ovarian cancer; risk estimates and CIs or calculable **Study design(s):** Case-control and cohort **Process for selection:** NR	**Data extraction variables**: Study design, country, cancer grading (invasive or borderline) and cancer histotype, number of subjects, type of controls and period of enrolment, duration of follow-up, RR estimates and CIs, and variables adjusted for in the analysis. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risks **Assessment of heterogeneity**: Chi-squared and I^2 statistic **Assessment of publication bias**: Contour-enhanced funnel plot and Egger's test **Sensitivity analyses**: Conducted stratified analyses for study design, type of controls, study geographic area, cancer grading, cancer histotype, reference category and studies adjusting for the main potential confounding factors (age, parity and oral contraceptive use). **Dose-response analyses:** Used linear and non-linear meta regression models.	3.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Rota et al., 2012b	**Databases searched:** PubMed **Years searched**: Inception to Dec 2010 **Keywords/MESH terms**: Alcohol drinking, alcoholic beverages, prostate neoplasms **Other strategies**: Reference lists of potentially relevant articles screened **Limits**: English language	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Prostate cancer; risk estimates and CIs or calculable **Study design(s):** NR **Process for selection:** Three authors assessed potentially relevant articles	**Data extraction variables**: Study design, country, period of enrolment, number of participants, RR estimates and CIs for each level of alcohol consumption, and variables adjusted for in the analysis **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared and I^2 statistic **Assessment of publication bias**: Contour-enhanced funnel plot and Egger's test **Sensitivity analyses**: Excluded one study at a time from the analysis. Conducted subgroup analyses by study design, type of controls, study geographic area, reference category, and of studies adjusting for main potential confounding factors (age, race, and smoking). **Dose-response analyses:** Used a random effects meta-regression model in a nonlinear dose–response relationship framework to provide the best-fitting two-term fractional-polynomial model	3.5
Samokhvalov et al., 2010a	**Databases searched:** Medline, EMBASE, Web of Science, CINAHL, PsycInfo, ETOH, and Google Scholar **Years searched**: Jan 1960 to Sep 2008 **Keywords/MESH terms**: Alcohol, alcohol, alcohol consumption, alcohol intake, drinking, alcoholism, alcohol abuse, alcohol misuse, epilepsy, epileptic, seizures **Other strategies**: Major epidemiological journals and reference lists were reviewed manually. **Limits**: None	**Population(s):** NR **Exposure:** Three or more categories of alcohol consumption **Outcome(s):** Epilepsy morbidity or unprovoked seizures. Studies on primarily alcohol-induced seizures or seizures provoked by other factors were excluded. **Study design(s):** Case control or cohort study reporting hazard ratios, relative risks, or odds ratios **Process for selection:** NR	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane Q test, I^2 statistic **Assessment of publication bias**: Egger's test, Begg & Mazumdar test **Sensitivity analyses**: NR **Dose-response analyses:** Used methods proposed by Greenland and Longnecker to back calculate and pool risk estimates. First and second degree fractional polynomial models were fitted to derive the dose-response curve. The best fitting model was selected based on a closed test comparison and overall model fit assessed using the Q statistic.	5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Samokhvalov et al., 2010b	**Databases searched:** Medline, EMBASE, Web of Science, CINAHL, PsycINFO, ETOH and Google Scholar **Years searched**: Jan 1960 to Apr 2009 **Keywords/MESH terms**: Alcohol, alcohol consumption, alcohol intake, drinking, alcoholism, alcohol abuse alcohol misuse, rhythm, arrhythmia, dysrhythmia, tachyarrhythmia, bradyarrhythmia, tachycardia, bradycardia, conduction, fibrillation, flutter, atrial, ventricular, paroxysmal, exstrasystol. Performed additional broad search using keywords atrial fibrillation, rhythm and 'risk factor'. **Other strategies**: Major epidemiological journals and reference lists were reviewed manually. **Limits**: None	**Population(s):** NR **Exposure:** Three or more categories of alcohol consumption **Outcome(s):** Medically diagnosed onset of atrial fibrillation verified by ECG data (according to the diagnostic criteria of the International Statistical Classification of Diseases) **Study design(s):** Case control or cohort studies **Process for selection:** One reviewer assessed inclusion based on titles and abstracts; potentially eligible studies were screened jointly by two reviewers.	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane Q-statistic, I^2 statistic **Assessment of publication bias**: Visual inspection of Begg's funnel plot, Begg–Mazumdar test and Egger test **Sensitivity analyses**: NR **Dose-response analyses:** Used methods proposed by Greenland and Longnecker to back calculate and pool risk estimates. First and second degree fractional polynomial models were fitted to derive the dose-response curve. The best fitting model was selected based on a closed test comparison and overall model fit assessed using the Q statistic.	6
Samokhvalov et al., 2010c	**Databases searched:** Medline, EMBASE, Web of Science, ETOH and AIM **Years searched**: Jan 1980 to Aug 2009 **Keywords/MESH terms**: Alcohol, alcohol consumption, alcohol intake, ethanol, alcoholism, heavy drinking, pneumonia. **Other strategies**: Reviewed reference lists of identified studies and review articles. **Limits**: None	**Population(s):** NR **Exposure:** alcohol consumption **Outcome(s):** Morbidity and/or mortality related to community-acquired pneumonia. (Diagnoses had to meet ICD criteria: 480–486 in ICD-8, 481–486 in ICD-9 and J10–J18 in ICD-10). **Study design(s):** Case control or cohort study **Process for selection:** NR	**Data extraction variables**: Study details, sample size, country, region, ethnicity, age, sex, endpoints, adjustments, study design, methods of interview, time-period of alcohol consumption, response rates, and RRs and corresponding 95% CIs for each category of alcohol consumption. **Process for data extraction**: Independently undertaken by two reviewers, differences were resolved with help of a third reviewer. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Cochrane Q statistic, I^2 statistic **Assessment of publication bias**: Egger's test and Begg-Mazumdar test **Sensitivity analyses**: Excluded a dataset that contributed 60% of the total number of participants. **Dose-response analyses:** Used methods proposed by Greenland and Longnecker to back calculate and pool risk estimates. First and second degree fractional polynomial models were fitted to derive the dose-response curve. The best fitting model was selected based on a closed test comparison and overall model fit assessed using the Q statistic.	5.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Song et al., 2012	**Databases searched:** PubMed, EMBASE, Medline **Years searched**: Inception to Aug 2011 **Keywords/MESH terms**: Alcohol, wine, beer, liquor, ethanol, spirit, renal cell carcinoma, kidney cancer, renal cell cancer, renal adenocarcinoma, kidney adenocarcinoma **Other strategies**: Screened references from retrieved articles **Limits**: English language	**Population(s):** NR **Exposure:** Total alcoholic beverage or specific alcoholic beverage intake **Outcome(s):** Incident renal cell, kidney cancer, renal, or kidney adenocarcinoma; risk estimates and CIs **Study design(s):** Cohort and case-control **Process for selection:** Two authors independently assessed eligibility	**Data extraction variables**: Reference details, publication year, country, study design, study period, participants' age and sex, endpoint, exposure assessment, and the number of cases and controls or person–years for each category of alcoholic beverage intake and covariates for adjustment in the analysis **Process for data extraction**: NR **Details of QA tool/checklist**: Newcastle-Ottawa scale **Process for quality assessment**: Each study was assessed independently by two authors and scores averaged. Discrepancies in >1 score between two authors were resolved by consensus	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistic. A meta-regression analysis investigated the association by study design, sex, smoking adjustment or hypertension adjustment. **Assessment of publication bias**: Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** Examined the non-linearity of the relationship using restricted cubic splines.	5
Sun et al., 2011	**Databases searched:** Medline, EMBASE **Years searched**: Inception to Apr 2010 **Keywords/MESH terms**: Alcohol, beer, wine, liquor, lifestyle, endometrial cancer, uterine corpus cancer, endometrial carcinoma **Other strategies**: References of retrieved articles screened **Limits**: English language	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Endometrial cancer incidence or mortality, and RR/OR estimates **Study design(s):** Prospective or case-control; adjusted for potential endometrial cancer risk factors e.g. age, BMI, or parity **Process for selection:** Conducted independently by two authors	**Data extraction variables**: Reference details, year of publication, country, years of follow-up or study period, study design, type of controls, age range of participants, sample size, exposure of alcohol consumption, type of alcoholic beverage, covariates, risk estimates and 95% CI; most completely adjusted estimate was extracted. **Process for data extraction**: Data extracted independently by two researchers **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random-effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistic **Assessment of publication bias**: Egger's test **Sensitivity analyses**: Assessed location of the study (US vs. other countries), and adjustment for hormone replacement therapy (HRT) use **Dose-response analyses:** NA	5.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Taylor et al., 2009	**Databases searched:** Medline, EMBASE, CINAHL, PubMED, CABS (BIDS), WHOLIST, SIGLE, ETOH, Alcohol In Moderation and Web of Science **Years searched**: 1980 to Jan 2008 **Keywords/MESH terms**: Alcohol, ethanol, hypertension, hypertensive, case control, cohort, prospective), risks. **Other strategies**: Reference lists of retrieved studies were reviewed. **Limits**: None	**Population(s):** NR **Exposure:** At least three levels of alcohol consumption **Outcome(s):** Hypertension (physiological measures, self-report of doctor-diagnosed hypertension or reported use of hypertensive medication were accepted for outcome ascertainment) **Study design(s):** Case control or cohort study **Process for selection:** NR	**Data extraction variables**: Levels of alcohol exposure, number of cases within each exposure level, total population at risk at each exposure level, adjusted estimates of RR and corresponding 95% confidence intervals **Process for data extraction**: Duplicate extraction undertaken on random sample of 15 studies. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q and I^2 statistic **Assessment of publication bias**: Begg-Mazumdar test, Egger's test and 'trim and fill' method. **Sensitivity analyses**: NR **Dose-response analyses:** Best-fitting curves were estimated using linear, first-order and second-order fractional polynomial regression; assessed using standard goodness of fit statistics. Comparison of curves was made using a chi-squared distribution.	5.5
Taylor et al., 2010	**Databases searched:** Medline, EMBASE, CINAHL, PubMed, CABS (BIDS), WHOKIST, SIGLE, ETOH, Alcohol in Moderation, Web of Science. **Years searched:** Jan 1980 to Nov 2008 **Keywords/MESH terms**: Alcohol, case control, case crossover, risk, injury, motor vehicle accidents, poisonings, falls, suicide, homicide, drowning **Other strategies**: Reference lists of retrieved studies were reviewed **Limits**: None.	**Population(s):** NR **Exposure:** Acute alcohol consumption **Outcome(s):** Injury (adopted a broad definition with no strict adherence to ICD codes or other diagnostic criteria required) **Study design(s):** Case control or case crossover study **Process for selection:** NR	**Data extraction variables**: Level of alcohol exposures in each study, number of cases at each exposure level, total population at risk at each exposure level, adjusted estimates of relative risk and corresponding 95% confidence intervals. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q-statistic, I^2 statistic **Assessment of publication bias**: Begg-Mazumdar test, Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** Best-fitting curves were estimated using linear, first-order and second-order fractional polynomial regression; assessed using standard goodness of fit statistics. Comparison of curves was made using a chi-squared distribution.	5.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Taylor & Rehm, 2012	**Databases searched:** Medline, EMBASE, CINAHL, PubMED, Google Scholar, CABS,WHOLIST, SIGLE, ETOH, Alcohol in Moderation, and Web of Science **Years searched**: Jan 1980 to Dec 2010 **Keywords/MESH terms**: Alcohol, case control, case crossover, risk, injury, motor vehicle accidents **Other strategies**: Reference lists of retrieved studies were reviewed **Limits**: None	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Fatal motor vehicle injury (adopted a broad definition with no strict adherence to ICD codes or other diagnostic criteria required) **Study design(s):** Case control and cohort study **Process for selection:** NR	**Data extraction variables**: Level of alcohol exposures in each study, number of cases at each exposure level, total population at risk at each exposure level, adjusted estimates of relative risk or odds ratios and corresponding 95% confidence intervals. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Q-statistic, I^2 statistic **Assessment of publication bias**: Begg-Mazumdar test, Egger's test **Sensitivity analyses**: Post hoc sensitivity analysis performed to test whether the inclusion of six separate data sets had any more influence over the pooled estimate than one aggregated data set **Dose-response analyses:** Used linear and first-order fractional polynomial regression of the inverse-variance weighted data to estimate a best fitting curve; assessed using standard goodness of fit statistics. Comparisons of curves were made using a chi-square distribution.	4
Tramacere et al., 2010a	**Databases searched:** PubMed **Years searched**: Inception to Sep 2009 **Keywords/MESH terms**: Alcohol, mouth, oral, pharynx, pharyngeal, cancer, carcinoma, neoplasm **Other strategies**: Reference lists of potentially relevant articles screened **Limits**: NR	**Population(s):** NR **Exposure:** At least three levels of alcohol consumption **Outcome(s):** Oral and pharyngeal cancers; risk estimate and CIs or calculable **Study design(s):** Case-control and cohort **Process for selection:** Three authors assessed potentially relevant papers	**Data extraction variables**: Study design, country, number of subjects, duration of follow-up and type of controls, sex, variables adjusted for in the analysis, RR estimates for categories of alcohol drinking and the corresponding 95% CIs and the number of cases and non-cases or person-years for each level of alcohol consumption. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared **Assessment of publication bias**: NR **Sensitivity analyses**: Examined influence of studies using: (i) a reference category different from non- or occasional drinkers; (ii) reporting estimates not adjusted for the main risk factors (i.e. sex, age and smoking); and (iii) studies in which the SE was computed by multiplying the crude SE by 1.5. **Dose-response analyses:** Used a random-effects meta-regression model in a non-linear dose–response relationship framework to provide the best fitting two-term fractional–polynomial model	3

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Tramacere et al., 2012a	**Databases searched:** PubMed **Years searched**: Inception to June 2010 **Keywords/MESH terms**: Alcohol drinking, alcoholic beverages, stomach neoplasms **Other strategies**: Reference lists of potentially relevant articles screened **Limits**: English language	**Population(s):** NR **Exposure:** NR **Outcome(s):** OR/RR and 95% CI **Study design(s):** Case-control and cohort **Process for selection:** Three authors assessed potentially relevant papers	**Data extraction variables**: Study design, country, number of subjects (cases, controls or cohort size), type of controls and period of enrolment, duration of follow-up, cancer site, sex distribution of the study population, variables adjusted for in the analysis, RR estimates and CIs, number of cases and non-cases or person-years for each category of alcohol consumption **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared test; I^2 statistic **Assessment of publication bias**: Contour enhanced funnel plot, Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** Used a random-effects meta-regression model in a nonlinear dose–response relationship framework to provide the best-fitting two-term fractional-polynomial model	4
Tramacere et al., 2010b	**Databases searched:** PubMed **Years searched**: Inception to Mar 2009 **Keywords/MESH terms**: Alcohol, pancreas, pancreatic, cancer, carcinoma, neoplasm **Other strategies**: Checked reference list of all papers of interest **Limits**: English language	**Population(s):** NR **Exposure:** At three levels of alcohol consumption **Outcome(s):** Pancreatic cancer; risk estimates and CIs or calculable **Study design(s):** Case-control and cohort **Process for selection:** Two authors assessed potentially relevant articles	**Data extraction variables**: Study design, country, number of subjects, period of enrolment or follow-up, sex, confounders controlled for in the analysis, risk estimates and CIs, and the number of cases and non-cases for each level of alcohol consumption. **Process for data extraction**: NR **Details of QA tool/checklist**: Quality of each study assessed using following criteria: study design (3 questions), assessment of alcohol drinking (4 questions) and analysis (3 questions). An overall quality score was obtained for each study (range 0 to 10). **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared; used random effects model when significant heterogeneity was found. **Assessment of publication bias**: NR **Sensitivity analyses**: Calculated summary estimates in strata of sex, study design, geographic area, quality score, and allowance for tobacco smoking. **Dose-response analyses:** Used a random-effect meta-regression model in a non-linear dose-response relationship framework, which provided the best fitting two-term fractional-polynomial model.	4

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Tramacere et al., 2012b	**Databases searched:** PubMed **Years searched**: Inception to Oct 2010 **Keywords/MESH terms**: Alcohol drinking, alcoholic beverages, stomach neoplasms, esophageal neoplasms **Other strategies**: Reference lists of potentially relevant articles screened **Limits**: English language	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Oesophageal and/or gastric cardia adenocarcinoma; risk estimate and CIs or calculable **Study design(s):** Case-control and cohort **Process for selection:** Three authors assessed potentially relevant papers	**Data extraction variables**: Study design, country, gender, categories of alcohol intake considered, RR estimates and 95% CIs, adjustment variables and the number of cases and non-cases or person-years for each category of alcohol consumption **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared and I^2 statistic **Assessment of publication bias**: Contour-enhanced funnel plot, Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** Used a random effects meta-regression model in a nonlinear dose–response relationship framework, to choose the best-fitting two-term fractional-polynomial model	4
Tramacere et al., 2012c	**Databases searched:** PubMed **Years searched**: up to January 2011 **Keywords/MESH terms**: 'Alcohol drinking' or 'alcohol beverages' and 'lymphoma'. **Other strategies**: None **Limits**: English language only.	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Hodgkin lymphoma **Study design(s):** Case control and cohort study reporting relative risk or odds ratio **Process for selection:** NR	**Data extraction variables**: Study design, country, sex, cancer type, number of participants, types of controls, period of enrolment, duration of follow up, RR estimates and 95% CIs, adjustment variables. **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Relative risk **Assessment of heterogeneity**: Chi-squared test and I^2 statistic **Assessment of publication bias**: Begg-Mazumdar test, Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** Used a random effects meta-regression model in a nonlinear dose–response relationship framework, to choose the best-fitting two-term fractional-polynomial model	4.5

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis	AMSTAR rating
Zeisser et al., 2013	**Databases searched:** Medline, PsycINFO **Years searched**: 1970 to 2009 **Keywords/MESH terms**: Emergency room, emergency department, accident and emergency and alcohol, drinking, alcohol drinking. Broad results so refined search to focus on injury **Other strategies**: Searches of online journals, reference lists and internet search (Google, Google Scholar and the National Drug Research Institute). Key national and international researchers were contacted. **Limits**: Peer-reviewed studies published in English.	**Population(s):** Samples drawn specifically from Emergency Department populations **Exposure:** Self-reported alcohol use within 6 hours of injury **Outcome(s):** Injury (applied a broad, general definition without strict adherence to ICD codes or diagnostic criteria). **Study design(s):** Case control or case crossover study **Process for selection:** NR	**Data extraction variables**: Sample, study characteristics, demographics, nature of injury(s), alcohol consumption **Process for data extraction**: Two reviewers independently coded the studies and matching and control variables. All coding discrepancies were discussed in detail. A third reviewer checked the coding sheet for accuracy, completeness, and consistency; any discrepancies were discussed until resolved. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Odds ratio **Assessment of heterogeneity**: Q-statistic **Assessment of publication bias**: Funnel and precision plots and regression analysis (Egger's test). **Sensitivity analyses**: Meta-regression examined impact of study design and alcohol consumption recall period, and gender. **Dose-response analyses:** NA	5
Zhu et al., 2012	**Databases searched:** Medline **Years searched**: NR **Keywords/MESH terms**: NR **Other strategies**: NR **Limits**: Full published English-language papers.	**Population(s):** NR **Exposure:** Alcohol consumption **Outcome(s):** Psoriasis **Study design(s):** Case control studies reporting odds ratios **Process for selection:** NR	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Odds ratio **Assessment of heterogeneity**: Chi-squared **Assessment of publication bias**: Egger's test, visual inspection of funnel plots **Sensitivity analyses**: One-way sensitivity analyses **Dose-response analyses:** NA	3

Table 13. Summary of methods: Mendelian randomisation approach

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis
Chen et al., 2008b	**Databases searched:** Medline, Web of Knowledge **Years searched**: Up to Oct 2006 **Keywords/MESH terms**: Aldehyde dehydrogenase 2, ALDH2, hypertension, blood pressure, cardiovascular diseases, coronary disease, heart disease, coronary artery disease **Other strategies**: Reviewed bibliographies of retrieved articles. **Limits**: None	**Population(s):** Individuals with *ALDH2* genotype **Exposure:** Alcohol consumption **Outcome(s):** Systolic or diastolic blood pressure, hypertension **Study design(s):** NR **Process for selection:** Undertaken independently by two reviewers.	**Data extraction variables**: First author's name, year of publication, country and city in which the study was performed, name of the study, study design, number and source of participants, sex, method of assessment of drinking status, categories of alcohol drinking, mean alcohol drinking and standard deviation by ALDH2 genotype, distribution of potential confounding factors by genotype with p-values, distribution of genotypes among hypertensive and non-hypertensive participants, mean blood pressure and standard deviation by ALDH2 genotype, and reported effect estimates and 95% confidence intervals for ALDH2 genotype and hypertension risk. **Process for data extraction**: Used a standard protocol for data extraction. Carried out independently by two reviewers. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; fixed effects model. Estimates of the causal effect of alcohol on blood pressure were calculated using standard instrumental variable estimation methods. Instrument strength was assessed using the first-stage F-statistic. **Measure of effect:** Odds ratio (hypertension); mean difference (blood pressure) **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Egger's test, Begg-Mazumdar test **Sensitivity analyses**: Repeated instrumental variable estimation analysis assuming a correlation of 0.2 in all genotypes and all studies. **Dose-response analyses:** NA
Lewis & Davey Smith, 2005	**Databases searched:** Medline, Web of Knowledge **Years searched**: Up to Mar 2004 **Keywords/MESH terms**: oesophageal, esophageal, ALDH2, aldehyde dehydrogenase **Other strategies**: Cited reference search of retrieved articles and reviewed bibliographies of retrieved articles **Limits**: NR	**Population(s):** Individuals with *ALDH2* genotype **Exposure:** Alcohol consumption **Outcome(s):** Oesophageal cancer **Study design(s):** NR **Process for selection:** NR	**Data extraction variables**: NR **Process for data extraction**: NR **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Meta-analysis; random effects model **Measure of effect:** Odds ratio **Assessment of heterogeneity**: I^2 statistic **Assessment of publication bias**: Egger's test **Sensitivity analyses**: NR **Dose-response analyses:** NA

Reference	Search strategy	Inclusion criteria	Data extraction and QA	Methods of analysis
Wang et al., 2011	**Databases searched:** Medline, EMBASE **Years searched**: Up to May 2010 **Keywords/MESH terms**: Colorectal neoplasia, colon neoplasia, rectal neoplasia; ALDH2 or aldehyde dehydrogenase 2; gene or polymorphism. **Other strategies**: Reviewed bibliographies of retrieved articles. **Limits**: NR	**Population(s):** Individuals with *ALDH2* genotype **Exposure:** Alcohol intake **Outcome(s):** Colorectal neoplasia **Study design(s):** NR **Process for selection:** NR	**Data extraction variables**: First author's name, year of publication, country and city in which the study was performed, age, gender, number and source of participants, 487Lys allele frequency in controls and drinking status by ALDH2 genotype. **Process for data extraction**: Two reviewers independently extracted data from each article. Discrepancies were resolved by discussion until consensus was achieved. **Details of QA tool/checklist**: NR **Process for quality assessment**: NR	**How were studies combined**: Cumulative and recursive cumulative meta-analyses; fixed effects models unless evidence of heterogeneity **Measure of effect:** Odds ratio **Assessment of heterogeneity**: Q statistic. I^2 statistic **Assessment of publication bias**: Egger's test, Begg–Mazumdar test **Sensitivity analyses**: Limited to studies including >500 individuals. **Dose-response analyses:** Not applicable

Table 14. Summary of methods: Pooled data analyses

Reference	Source of study data	Inclusion criteria for sites	Data collection	Methods of analysis
Borges et al., 2006	**Project title:** Emergency Room Collaborative Alcohol Analysis Project (ERCAAP); WHO Collaborative Study on Alcohol and Injuries (WHO-ER) **Years of data collection:** 1994-2002 (ERCAAP); 2001-2002 (WHO-ER) **Number of data sites**: 16 (ERCAAP); 12 (WHO-ER) **Countries**: Argentina, Australia, Canada, Mexico, Poland, Spain, USA (ERCAAP); Argentina, Belarus, Brazil, Canada, China, Czech Republic, India, Mexico, Mozambique, South Africa, Sweden, New Zealand (WHO-ER).	**Population(s):** All patients aged 18 and older admitted to the emergency room. **Exposure:** Self-reported alcohol consumption in the 6 hours prior to the injury or illness event; blood alcohol concentration (BAC) estimate. Injured patients who reported drinking after the event and had a positive BAC were excluded. **Outcome(s):** Injury **Process for selection of sites:** NR	**Data collected**: Reason for ER visit, self-reported alcohol consumption in the 6 hours prior to the injury or illness event, quantity and frequency of usual drinking during the last year, demographic characteristics, BAC, per capita consumption of ethanol, legal drinking age, legal level of intoxication while driving, ER type and level of trauma care. **Process for data collection**: NR	**Measure of effect:** Relative risk (RR) **Calculation of effect size:** Case-crossover method was used taking into account the amount of expected person-time exposure to alcohol. The numerator of the RR was the summation of unexposed hours in the control period (last 12 months) among the injury cases who reported exposure during the hazard period (6-hour prior). The denominator of the RR was the summation of exposed hours in the control period (last 12 months) among the injury cases that reported no exposure during the hazard period (6-hour prior). **How were studies combined**: Meta-analysis; fixed and random effects model **Assessment of heterogeneity**: Chi-squared **Sensitivity analyses**: Meta-regression examined the influence of site-level contextual variables.
Cherpitel et al., 2003b 2003c	**Project title:** Emergency Room Collaborative Alcohol Analysis Project **Years of data collection:** 1984-1997 **Number of data sites**: 30 emergency rooms **Countries**: USA, Mexico, Canada, Australia, Spain, Italy	**Population(s):** All patients aged 18 and older admitted to the emergency room. **Exposure:** Self-reported alcohol consumption in the 6 hours prior to the injury or illness event; blood alcohol concentration (BAC) estimate. Injured patients who reported drinking after the event and had a positive BAC were excluded. **Outcome(s):** Injury **Process for selection of sites:** Selected by the country investigator on the basis of the size of geographic area and population density covered by the emergency room.	**Data collected**: Reason for ER visit, self-reported alcohol consumption in the 6 hours prior to the injury or illness event, quantity and frequency of usual drinking during the last year, demographic characteristics, BAC, per capita consumption of ethanol, legal drinking age, legal level of intoxication while driving, ER type and level of trauma care. **Process for data collection**: Standard 25-minute questionnaire	**Measure of effect:** Odds ratio **Calculation of effect size:** Linear logistic regression controlling for gender and age and for gender, age and consuming five or more drinks on an occasion at least monthly (5+ monthly). **How were studies combined**: Meta-analysis; fixed and random effects model **Assessment of heterogeneity**: Q-statistic **Sensitivity analyses**: Analyses were repeated with highly influential ERs removed. Meta-regression examined the influence of site-level contextual (organizational and socio-cultural) variables.

Reference	Source of study data	Inclusion criteria for sites	Data collection	Methods of analysis
Collaborative Group on Hormonal Factors in Breast Cancer, 2002	**Project title:** Collaborative Group on Hormonal Factors in Breast Cancer **Years of data collection:** 1984-2001 **Number of data sites/studies**: 65 **Countries**: USA, Canada, The Netherlands, UK, Australia, Denmark, New Zealand, Slovenia, Germany, Italy, France, Greece, and other countries not specified	**Population(s):** NR **Exposure:** Alcohol intake **Outcome(s):** Incident invasive breast cancer **Study design:** Case control and cohort studies including at least 100 women **Process for selection of sites/studies:** NA	**Data collected**: NR **Process for data collection**: NR	**Measure of effect:** Relative risk **Calculation of effect size:** Obtained from 'observed minus expected' values by the one-step method. All analyses were routinely stratified by study, and centre within study; by age; by parity and, where appropriate, age when the first child was born and age at first birth; and by smoking history. **How were studies combined**: Mantel-Haenszel stratification technique **Assessment of heterogeneity**: NR **Sensitivity analyses**: Dose-response relationship explored by fitting a linear trend in the log relative risk of breast cancer across increasing categories of consumption. In estimating such trends, the median consumption within a given category was taken to be the level of alcohol consumption for that category.
Freudenheim et al., 2005 Genkinger et al., 2006 Cho et al., 2004	**Project title:** Pooling Project of Prospective Studies of Diet and Cancer **Years of data collection:** 1980-1996 **Number of data sites/studies**: 7 **Countries**: NR	**Population(s):** NR. Participants excluded if they reported a history of cancer (other than non-melanoma skin cancer) at baseline. **Exposure:** Alcohol consumption **Outcome(s):** ≥50 incident cases of lung cancer **Study design:** Cohort studies **Process for selection of sites/studies:** NA	**Data collected**: NR **Process for data collection**: Follow-up questionnaires and review of medical records and linkages with cancer registries.	**Measure of effect:** Relative risk **Calculation of effect size:** Cox proportional hazards model; age at baseline and the year that the baseline questionnaire was returned were included as stratification variables. Adjusted for smoking status, smoking duration, amount smoked, education, body mass index, and energy intake. **How were studies combined**: Meta-analysis; random effects model. **Assessment of heterogeneity**: Q-statistic **Sensitivity analyses**: Tested whether there were differences in the RRs between the strata by using meta-regression. Reclassified never smokers in the highest drinking category as former smokers.

Reference	Source of study data	Inclusion criteria for sites	Data collection	Methods of analysis
Morton et al., 2005	**Project title:** International Lymphoma Epidemiology Consortium (InterLymph) **Years of data collection:** 1990-2004 **Number of data sites/studies**: 9 **Countries**: USA, Sweden, UK, Italy	**Population(s):** NR. Participants known to be HIV positive were excluded from analyses. **Exposure:** Alcohol consumption **Outcome(s):** Non-Hodgkin's lymphoma (NHL) **Study design:** Case control studies **Process for selection of sites/studies:** Voluntary case-control consortium established in 2000 to facilitate collaboration among major epidemiological studies of lymphoma worldwide.	**Data collected**: NR **Process for data collection**: NR	**Measure of effect:** Odds ratio **Calculation of effect size:** Unconditional logistic regression; controlled for age, sex, ethnic origin and socioeconomic status. **How were studies combined**: Meta-analysis; random effects model (inverse variance method) **Assessment of heterogeneity**: Chi-squared test **Sensitivity analyses**: NR
Purdue et al., 2009	**Project title:** International Head and Neck Cancer Epidemiology (INHANCE) Consortium **Years of data collection:** 1984-2006 **Number of data sites/studies**: 15 **Countries**: Italy, France, Switzerland, Central Europe, USA, Puerto Rico, Latin America, Spain, Ireland, Poland, Canada, Australia, Cuba, India, Sudan	**Population(s):** NR. Individuals with missing data on age, sex, or race/ethnicity, and participants from the India and Sudan centres were excluded. **Exposure:** Alcohol consumption (frequency of drinking, duration of drinking, and different types of alcoholic beverages consumed). **Outcome(s):** Oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, and head and neck cancer unspecified. Cancers of the salivary gland were excluded. **Process for selection of sites:** NR	**Data collected**: NR **Process for data collection**: Study interviews conducted face-to-face.	**Measure of effect:** Odds ratio **Calculation of effect size:** Unconditional logistic regression; controlled for age, gender, education, race/ethnicity, study centre, pack-years of cigarette smoking, years of cigar smoking, years of pipe smoking, and consumption frequency of other beverages.. **How were studies combined**: Two-stage random effects modelling approach **Assessment of heterogeneity**: Likelihood ratio tests **Sensitivity analyses**: Stratified by geographic region.

Table 15. Summary of AMSTAR measurement tool assessment

Author (Year)	AMSTAR measurement tool criteria											
	1	2	3	4	5	6	7	8	9	10	11	Score
Anstey et al., 2009	Can't answer	Yes	Yes	No	No	Yes	No	NA	Yes	No	Yes	5
Bagnardi et al., 2001	Can't answer	Can't answer	Yes	No	No	No	No	NA	Yes	No	No	2
Bagnardi et al., 2011	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Yes	Yes	4
Baliunas et al., 2009	Can't answer	No	Yes	No	No	Yes	No	NA	Yes	Yes	Yes	5
Balinuas et al., 2010	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Partial	No	2.5
Bay & Kesmodel, 2011	Can't answer	Can't answer	Yes	No	No	Yes	Yes	No	Can't answer	NA	No	3
Bellocco et al., 2012	Can't answer	Can't answer	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	6
Berg et al., 2008	Can't answer	Yes	Yes	No	No	Yes	Yes	Can't answer	Yes	No	No	5
Chen et al., 2008a	Can't answer	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Partial	No	6.5
Chong et al., 2008	Can't answer	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Partial	Yes	7.5
Corrao et al., 2004	Can't answer	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	6
Costanzo et al., 2011	Can't answer	Can't answer	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Di Castelnuovo et al., 2006	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	No	Yes	3
Fedirko et al., 2011	Can't answer	Can't answer	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	6
Henderson et al., 2007a; 2007b	Can't answer	Partial	Partial	No	No	Yes	Yes	Yes	Yes	NA	No	4
Irving et al., 2012	Can't answer	Can't answer	Yes	No	No	Yes	No	NA	Yes	Yes	Yes	5
Islami et al., 2010	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Yes	Yes	4

Author (Year)	AMSTAR measurement tool criteria											
	1	2	3	4	5	6	7	8	9	10	11	Score
Islami et al., 2011	Can't answer	Can't answer	No	No	No	No	No	NA	Yes	Yes	Yes	3
Kan et al., 2011	Can't answer	Partial	Yes	No	No	Yes	No	NA	Yes	Partial	No	4
Key et al., 2006	Can't answer	Can't answer	Yes	Yes	No	Yes	Yes	Yes	Yes	Partial	No	6.5
Kodama et al., 2011	Can't answer	Partial	Yes	No	No	Yes	No	NA	Yes	Yes	Yes	5
Kool et al., 2009*	Can't answer	Can't answer	Yes	Can't answer	Partial	Yes	Yes	Yes	Yes	Na	Yes	4.5
Latino-Martel et al., 2010	Can't answer	Can't answer	No	Can't answer	Yes	Yes	No	Na	Yes	Yes	Yes	5
Lönnroth et al., 2008	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Partial	Yes	3.5
Mao et al., 2010	Can't answer	Can't answer	Yes	No	Yes	Yes	No	NA	Yes	Yes	No	5
McCambridge et al., 2011	Can't answer	Yes	Yes	No	No	Yes	No	NA	Yes	NA	No	3
Parsons & Im, 2009	Can't answer	Partial	Partial	Can't answer	Can't Answer	Yes	No	NA	Yes	Partial	No	3.5
Patra et al., 2010	Can't answer	No	Yes	No	No	Yes	No	NA	Yes	Yes	Yes	5
Patra et al., 2011	Can't answer	Yes	Yes	Can't answer	No	No	No	Na	Yes	Yes	Yes	5
Pelucchi et al., 2012	Can't answer	Yes	No	No	No	Yes	No	NA	Yes	No	Yes	4
Peters et al., 2008	Can't answer	Yes	Yes	Can't answer	Partial	No	Partial	No	Yes	Partial	No	4.5
Rehm et al., 2010	Can't answer	Partial	Yes	Can't answer	Partial	Yes	No	NA	Yes	Yes	Yes	6
Roerecke & Rehm, 2010	Can't answer	No	Yes	No	No	Yes	No	Na	Yes	Partial	Yes	4.5
Roerecke & Rehm, 2011	Can't answer	No	Yes	Can't answer	No	Yes	No	Na	Yes	Partial	Yes	4.5
Rota et al., 2012a	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Partial	Yes	3.5

Author (Year)	AMSTAR measurement tool criteria											
	1	2	3	4	5	6	7	8	9	10	11	Score
Rota et al., 2012b	Can't answer	Partial	No	No	No	No	No	NA	Yes	Yes	Yes	3.5
Samokhvalov et al., 2010a	Can't answer	Can't answer	Yes	Can't answer	No	Yes	No	Na	Yes	Yes	Yes	5
Samokhvalov et al., 2010b	Can't answer	Partial	Yes	Can't answer	Partial	Yes	No	NA	Yes	Yes	Yes	6
Samokhvalov et al., 2010c	Can't answer	Partial	Yes	Can't answer	No	Yes	No	Na	Yes	Yes	Yes	5.5
Song et al., 2012	Can't answer	Partial	Yes	No	No	Yes	Yes	No	Yes	Partial	No	5
Sun et al., 2011	Can't answer	Yes	Yes	No	No	Yes	No	NA	Yes	Partial	Yes	5.5
Taylor et al., 2009	Can't answer	Partial	Yes	Can't answer	No	Yes	No	Na	Yes	Yes	Yes	5.5
Taylor et al., 2010	Can't answer	Can't answer	Yes	Can't answer	Partial	Yes	No	NA	Yes	Yes	Yes	5.5
Taylor & Rehm, 2012	Can't answer	No	Yes	Can't answer	No	Yes	No	Na	Yes	Yes	No	4
Tramacere et al., 2010a	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	No	Yes	3
Tramacere et al., 2010b	Can't answer	Can't answer	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Tramacere et al., 2012a	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Yes	Yes	4
Tramacere et al., 2012b	Can't answer	Can't answer	No	No	No	Yes	No	NA	Yes	Yes	Yes	4
Tramacere et al., 2012c	Can't answer	Can't answer	No	Can't answer	Partial	Yes	No	NA	Yes	Yes	Yes	4.5
Zeisser et al., 2013	Can't answer	Yes	Yes	Yes	No	No	No	Na	Yes	Yes	No	5
Zhu et al., 2012	Can't answer	Can't answer	No	Can't answer	No	Yes	No	No	Yes	Yes	No	3

Table 16. Assessment of publication bias

Study	Disease/health problem area	Methods used to assess publication bias	Findings from publication bias assessment
Bagnardi et al., 2011	Lung cancer	Egger's test	The asymmetry test for publication bias was not statistically significant.
Baliunas et al., 2009	Type II diabetes	Funnel plots; Egger and Begg tests	No significant publication bias was detected.
Balinuas et al., 2010	HIV infection	Egger and Begg tests	Both the Egger's and Begg's tests showed no publication bias (P = 0.526 and P = 0.067, respectively).
Chen et al., 2008a	Nasopharyngeal narcinoma	Funnel plots	Publication bias was not evident in the funnel plots. The authors note that publication bias may still be of concern because four studies were excluded that reported an association with alcohol drinking but did not present numeric data.
Chong et al., 2008	Age-related macular degeneration	Visual inspection of funnel plot	The funnel plot revealed asymmetry, suggesting that publication bias may be present. The authors suggested the presence of publication bias reflected an absence of studies with small sample sizes and small or null effects.
Costanzo et al., 2011	Fatal & non-fatal cardiovascular events	Inspection of funnel plots; Egger test	The funnel plot analysis was symmetrical for all categories of beer, spirit and wine intake, except for the lowest category of wine intake. Three studies which determined the asymmetry were excluded in subgroup analyses.
Fedirko et al., 2011	Colorectal cancer	Egger and Begg-Mazumdar tests, trim and fill method, and contour enhanced funnel plots	Authors note that the presence of publication bias was unlikely.
Irving et al., 2012	Pancreatitis	Visual inspection of Begg's funnel plot; Begg-Mazumdar and Egger tests	Both tests suggested no significant asymmetry of the funnel plot, indicating no evidence of substantial publication bias.
Islami et al., 2010	Laryngeal cancer	Begg and Mazumdar's test, Egger's test, funnel plots	No evidence of publication bias. The funnel plot and tests did not suggest significant publication bias.
Islami et al., 2011	Oesophageal squamous cell carcinoma	Begg's and Egger's tests	Egger's test was marginally significant for light alcohol drinking ($p<0.03$), however, the authors noted that the funnel plot was fairly symmetrical and did not suggest major publication bias. The funnel plot and Egger's weighted regression method did not suggest publication bias for moderate alcohol drinking. However, for heavy alcohol drinking, both the funnel plot and Egger's method ($p<0.004$) suggested significant publication bias. The authors report that the elimination of studies contributing to publication bias produced results that were qualitatively similar to those of prospective studies.
Kan et al., 2011	Extrahepatic bile system cancer	Begg's and Egger's tests	There was no evidence of publication bias.
Key et al., 2006	Breast cancer	Funnel plots	No evidence of publication bias.
Kodama et al., 2011	Atrial fibrillation	Visual inspection of a funnel plot; Begg and Egger tests; "trim and fill" procedure	Publication bias suggested for heavy alcohol consumption on visual inspection of the funnel plot, supported by Egger's test ($p>0.03$) but not Begg's test. Adjusted using the trim and fill method; inclusion of four negative unpublished results to produce a hypothetically symmetrical funnel plot modestly attenuated the pooled estimate for heavy alcohol consumption but it remained statistically significant ($p<0.001$).

Study	Disease/health problem area	Methods used to assess publication bias	Findings from publication bias assessment
Latino-Martel et al., 2010	Childhood leukemia	Funnel plots, Egger's test.	No evidence of publication bias. However, the authors note that 12 studies on risk factors of childhood leukemia, other than alcohol intake during pregnancy, in which maternal alcohol consumption was considered a potential confounder were excluded from the review.
Lönnroth et al., 2008	Tuberculosis	Funnel plots	Publication bias was suspected for high exposure studies, and three studies with the highest standard error excluded. Exclusion modestly attenuated the pooled relative risk but it remained statistically significant.
Mao et al., 2010	Bladder cancer	Egger and Begg tests.	No evidence of publication bias in any subgroup.
Parsons & Im, 2009	Benign prostatic hyperplasia	Egger's test, Begg-Mazumdar test.	No evidence of publication bias.
Patra et al., 2010	Stroke	Visual inspection of Begg's funnel plot; Begg–Mazumdar test and the Egger's test	Publication bias was not detected by either test.
Patra et al., 2011	Low birthweight, preterm birth and SGA	Visual inspection of Begg's funnel plot; Begg–Mazumdar test and the Egger's test	No evidence of publication bias.
Peters et al., 2008	Dementia and cognitive decline	Methods not reported.	Authors note that publication bias was not indicated by funnel plots and bias indicators were non-significant.
Rehm et al., 2010	Liver cirrhosis	Egger's test, Begg-Mazumdar test	Publication bias was not detected by either test.
Roerecke & Rehm, 2010	Ischaemic heart disease	Examined small study effects.	Peters et al.'s test did not indicate presence of publication bias or small-study effects. An adjusted effect that assumed the presence of publication bias corresponded to a pooled relative risk that was slightly lower than the effects found in the main meta-analyses.
Roerecke & Rehm, 2012	Ischaemic heart disease	'Peter's regression-based test'	Only one of the models showed evidence of publication bias (women, mortality at 12-24g/day). Sensitivity analyses omitting studies one by one and re-estimating the pooled RR did not reveal any substantial influence of a particular study on the pooled effect estimates.
Rota et al., 2012a	Ovarian cancer	Contour-enhanced funnel plot and Egger's test	No evidence of publication bias, no asymmetry according to the Egger's test.
Rota et al., 2012b	Prostate cancer	Contour-enhanced funnel plot and Egger's test	No evidence of publication bias, no asymmetry according to the Egger's test
Samokhvalov et al., 2010a	Unprovoked seizures and epilepsy	Egger's test, Begg & Mazumdar test	Visual inspections of the funnel plot and both tests revealed no significant asymmetry.
Samokhvalov et al., 2010b	Atrial fibrillation	Visual inspection of Begg's funnel plot, Begg–Mazumdar test and Egger test	The funnel plot and both tests showed no evidence of asymmetry.
Samokhvalov et al., 2010c	Pneumonia	Egger's test and Begg-Mazumdar test	No evidence of publication bias.
Song et al., 2012	Renal cell cancer	Egger's test	No evidence of publication bias.

Study	Disease/health problem area	Methods used to assess publication bias	Findings from publication bias assessment
Sun et al., 2011	Endometrial cancer	Egger's test	No evidence of publication bias.
Taylor et al., 2009	Hypertension	Begg-Mazumdar test, Egger's test and 'trim and fill' method.	Publication bias was not detected by either test.
Taylor et al., 2010	Injury	Begg-Mazumdar test, Egger's test	Publication bias was not detected by either test.
Taylor & Rehm, 2012	Fatal motor vehicle injury	Begg-Mazumdar test, Egger's test	Publication bias was detected by the Begg's ($p = 0.421$) and Egger's ($p = 0.032$) tests; visual inspection of the funnel plot showed scarcity of studies reporting lower or null effects.
Tramacere et al., 2012a	Gastric cancer	Contour enhanced funnel plot, Egger's test	No evidence of publication bias.
Tramacere et al., 2012b	Oesophageal and gastric cardia adenocarcinoma	Contour-enhanced funnel plot, Egger's test	No evidence of publication bias.
Tramacere et al., 2012c	Hodgkin lymphoma	Begg-Mazumdar test, Egger's test	No evidence of publication bias.
Zeisser et al., 2013	Injury	Funnel and precision plots and regression analysis (Egger's test).	The funnel plot indicated substantial asymmetry and therefore publication bias. The authors note that this asymmetry was largely attributable to one study with a large effect size and standard error (0.902). After exclusions of this study the funnel plot no longer showed evidence of significant publication bias.
Zhu et al., 2012	Psoriasis	Egger's test, visual inspection of funnel plots	No evidence of publication bias.

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