THE UNIVERSITY OF SYDNEY

Evaluating the evidence on the health effects of alcohol consumption

Technical report

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Contents

Abbreviations

AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AWC	Alcohol Working Committee
CI	confidence interval
FASD	fetal alcohol spectrum disorder
GI	gastro-intestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
IARD	International Alliance for Responsible Drinking
NHMRC	National Health and Medical Research Council
NOS	Newcastle-Ottawa Scale
NR	not reported
ROBIS	Risk of Bias in Systematic Reviews
RR	relative risk
OR	odds ratio
SIDS	sudden infant death syndrome
STI	sexually-transmitted infection

Background

Under Section 7 of the National Health and Medical Research Council Act 1992 (the NHMRC Act), NHMRC has responsibility for developing and issuing guidelines and health advice to the Australian community. As part of this role, in 2001, NHMRC issued the *Australian Alcohol Guidelines: Health Risks and Benefits* providing evidence-based guidance on reducing the health risks that arise from drinking alcohol to inform future policies and community materials. These guidelines were developed by NHMRC in collaboration with the Population Health Division of the then Australian Government Department of Health of Ageing (DoHA).

In March 2009, NHMRC released the *Australian Guidelines to Reduce Health Risks from Drinking Alcohol{NHMRC, 2009 #266}*, providing policy makers, health professionals and the Australian community with updated evidence-informed advice concerning the health risks of drinking alcohol. The guidelines provide universal guidance on reducing these risks applicable to healthy adults aged 18 years and over (Guideline 1 and 2), guidance specific to children and young people (Guideline 3) and to pregnant and breastfeeding women (Guideline 4).

This overview is the first stage being undertaken in the guideline update process. If gaps in evidence are identified, where no systematic reviews are found for an outcome, then the Alcohol Working Committee (AWC) will discuss if there is a need for an additional systematic review of primary studies for that outcome to be conducted.

Rationale for the review

NHMRC regularly reviews its guidelines to ensure that the advice is up to date and reflective of the latest evidence. At its 203rd session in March 2015, the Council of NHMRC recommended to NHMRC's Chief Executive Officer (CEO) that the 2009 Alcohol Guidelines be updated. Council agreed that the existing guidelines should remain in circulation until a decision is made by the CEO to release a final revised version of the guidelines.

The NHMRC has established the Alcohol Working Committee (AWC) to provide advice and guide the evaluation of evidence on the health effects of alcohol consumption. The AWC comprises experts in drug and alcohol research, epidemiology, biostatistics and modelling, addiction, mental health, clinical public health, fetal alcohol syndrome, Aboriginal and Torres Strait Islander health and consumer advocacy.

The purpose of this evidence evaluation is to update the evidence on the health effects of alcohol consumption to assist the NHMRC and AWC to update guidance on the health benefits and harms of alcohol consumption.

Objectives of the review

To undertake four reviews of systematic reviews (the overview), to evaluate evidence on:

1. The short term health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) associated with any single episode of drinking in the general population.
2. The long term health risks and benefits associated with varying levels and/or patterns of alcohol consumption (including no alcohol consumption) in the general population.

3. The health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) for pregnant women and their fetuses, including longer term effects on babies and children exposed in utero.
4. The health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) for breastfeeding women and their babies

Methods and limitations

Conducting an overview of systematic review-level evidence is a relatively recent methodology developed in response to the growing number of systematic reviews being published{Bastian, 2010 #3} and the need to develop more rapid methods for undertaking evidence synthesis. However, overviews of systematic reviews present several unique challenges{Pieper, 2012 #4}. Guidance on the latter stages of overviews of systematic reviews (quality assessment, collection and analysis of data, and overall assessment of the evidence) is particularly lacking{Pollock, 2016 #10}.

In an attempt to overcome some of these challenges, this overview implemented a number of methods to ensure methodological rigor of the overview. These methods are a combination of novel approaches and previously proposed approaches and were agreed at the protocol stage with NHMRC and the AWC.

Development of the research question

The PEO (Population, Exposure/Comparison, Outcome) criteria were used to develop the research questions for this evaluation. This involved focusing the question on the following elements:

- The target population(s) for the exposure
- The exposure(s) and comparator(s) being considered
- The health outcomes that are most relevant to assess

There were four research questions:

1. What are the short term health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) associated with any single episode of drinking in the general population?
2. What are the long term health risks and benefits associated with varying levels and/or patterns of alcohol consumption (including no alcohol consumption) in the general population?
3. What are the health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) for pregnant women and their fetuses, including longer term effects on babies and children exposed in utero?
4. What are the health risks and benefits of varying levels and/or patterns of alcohol consumption (including no alcohol consumption) for breastfeeding women and their babies?

These questions were specified in the statement of requirement. Note that the exposure and comparator are considered together as a combined element, in order to allow evidence that has categorised alcohol consumption in different ways to be considered. The PEO criteria for the research questions are outlined in Table 1, Table 2, Table 3, and Table 4.

Table 1: PEO criteria for the evaluation of research question 1

Element	Criteria
Population	The general population If evidence is identified, the following specific subpopulations will be examined: Sex Elderly (people ≥65 years) Youth (people < 18 years and between 18 - 25 years) People with existing mental and physical illnesses People with strong family history of alcohol dependence People on medicines or other drugs (prescribed and illicit) including interactions
Exposure and comparator	Varying levels and/or patterns of alcohol consumption (including no alcohol consumption) in a single episode or drinking occasion
Outcomes	Injury to self (including physical and domestic violence, road traffic accidents, falls, fire / burns, occupational and drowning, self-harm and poisoning) Acute cardiovascular events (including acute myocardial infarction, ischaemic stroke, haemorrhagic stroke, cardiac arrest and arrhythmia) Acute exacerbation of a mental illness STI Harmful alcohol-drug interactions Sexual function Acute GI (gastritis, reflux) Hangover

Table 2: PEO criteria for the evaluation of research question 2

Element	Criteria
Population	The general population If evidence is identified, the following specific subpopulations will be examined: Sex Elderly (people ≥65 years) Youth (people < 18 years and between 18 - 25 years) People with existing physical and mental health conditions that place them at a higher risk (including cancer, hepatitis B,C, or D, HIV, obesity, mental illness) People with strong family history of alcohol dependence People on medicines or other drugs (prescribed and illicit)
Exposure and comparator	Varying levels and/or patterns of alcohol consumption (including no alcohol consumption)
Outcomes	All-cause mortality and morbidity Cancer (including head and neck, breast, live, colorectal, oesophageal, gastric, skin, and prostate) Cardiovascular disease including hypertension, stroke, cardiac failure, cardiomyopathy and arrhythmias Liver disease including cirrhosis Alcohol-related pancreatitis Mental health disorders (including depression, anxiety and alcohol-related psychosis) Alcohol use disorders/dependence/withdrawal syndrome Diabetes and insulin resistance Obesity/overweight Quality of life Sleep disorders Central neurological disorders Cognitive impairment/dementia (including Korsakoff's syndrome) Seizures (as a co-morbidity) Fertility Osteoporosis (+/- fracture, bone healing) Gout Thiamine deficiency Peripheral neurological disorders e.g. neuropathy Gastro-oesophageal reflux Respiratory diseases Hormonal disorders

Table 3: PEO criteria for research question 3

Element	Criteria
Population	Pregnant women and their fetuses, babies and children
Exposure and comparator	Varying levels and/or patterns of alcohol consumption (including no alcohol consumption)
Outcomes	Fetal alcohol spectrum disorders (FASD) Low birth weight Small for gestational age Developmental delay Birth defects Stillbirth Behavioural problems Neonatal withdrawal Premature birth Spontaneous abortion and miscarriage

Table 4: PEO criteria for research question 4

Element	Criteria
Population	Breastfeeding women and their babies
Exposure and comparator	Varying levels and patterns of alcohol consumption (including no alcohol consumption)
Outcomes	Cognitive impairment in breastfeeding babies Sudden infant death syndrome (SIDS) Sedation in breastfeeding babies Child neglect/bonding Failure to thrive.

Initial scoping search

An initial scoping search was conducted to identify existing overviews of systematic reviews on the topic. These overviews can be used to inform the approach, understand the breadth of the topic and ensure we are not duplicating existing work.

Three overviews of systematic reviews on this topic were identified:

- Jones L, McCoy E et al. (2013) CMO Alcohol Guidelines: Mapping systematic review level evidence.{Jones, 2013 #13} Available at: **http://www.cph.org.uk/publication/cmo-alcohol-guidelines-review-mapping-systematic-review-level-evidence/**
- Newbury-Birch D, Gilvarry E et al. (2008) Impact of alcohol consumption on young people: a review of reviews.{Newbury-Birch, 2008 #14} Available at: **https://www.education.gov.uk/consultations/downloadableDocs/Review%20of%20existing%20reviews%20(Full).pdf**
- Alcohol Consumption and Risk of Cancer: a Systematic Literature Review{de Menezes, 2013 #12}

The report for the UK Chief Medical Officer{Jones, 2013 #13} is highly relevant as it was used to inform revision to the UK Alcohol guidelines. However, the inclusion criteria are broader than the review questions developed in this protocol and the report summarised the risk estimates for the included systematic reviews in tables but did not make any narrative conclusions or summary.

The report on the Impact of alcohol consumption on young people{Newbury-Birch, 2008 #14} reviewed the evidence on the harms and benefits of alcohol consumption for young children and adolescents. This is a subpopulation being considered by this protocol.

The systematic review of {de Menezes, 2013 #12@@author-year} was a review of meta-analyses examining alcohol consumption and cancer. This is one outcome being considered by this protocol.

None of the overviews identified in the scoping search are sufficiently recent or comprehensive to utilise as a basis for this research.

Literature search strategies

Searching electronic databases

Comprehensive systematic literature searches were undertaken on the 5th of January 2017 to identify all published systematic reviews published since January 2007 relevant to the review questions. Papers published after this date were not considered for inclusion in the overview. Individual searches were not carried out for each questions, as outcomes and population were not included as search terms, therefore only one search was undertaken for all questions. Outcomes were not included as search terms because they are often poorly indexed with controlled vocabulary terms in medical databases{Higgins, 2011 #6925} which then would result in relevant references would being missed. We searched the following databases using the search strategy in Table 5:

- Medline and Pre-MEDLINE using OVID SP
- EMBASE
- PsycINFO
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects
- Health Technology Assessment Database
- Joanna Briggs Institute (JBI) Database of Systematic Reviews, and
- Epistemonikos.

To identify systematic reviews providing evidence produced since the 2007 systematic review which informed the 2009 Alcohol Guidelines, the search will be conducted from 1st January 2007 onwards. However, it should be noted that search date of the systematic review is a more accurate indicator of its currency than its publication date, and that the currency of the systematic review is included as a criterion for inclusion in the overview.

The syntax of the search strategy was modified in each database as required.

Table 5: Search strategy for MEDLINE via Ovid

1	medline.tw.
2	meta-analysis.pt.
3	(systematic$ and (review$ or overview$)).tw.
4	meta?analy$.tw.
5	meta analy$.tw.
6	or/1-5
8	exp Alcohol drinking/
9	exp Alcoholic Beverages/
10	Alcoholism/ or Alcohol-Related Disorders/
11	Alcoholic Intoxication/
12	exp Binge Drinking/
13	exp Fetal Alcohol Spectrum Disorders/
14	alcohol*.ti,ab.
14	or/7-13
15	6 and 14
16	limit 15 to (humans and yr="2007 -Current")

Searching other resources

The reference lists of overviews of systematic reviews identified in the scoping search and the database search will be searched for additional relevant publications.

A search of the grey literature will be undertaken including, but not limited to, the following websites:

- Register of Australian Drug and Alcohol Research (http://www.radar.org.au/)
- National Drug and Alcohol Research Centre (http://ndarc.med.unsw.edu.au/)
- National Drug Research Institute (http://ndri.curtin.edu.au/)
- Australian Centre for Addiction Research (http://www.acar.net.au/)
- National Institute of Health and Care Excellence (https://www.nice.org.uk/)
- Agency for Healthcare Research and Quality (http://www.ahrq.gov/)
- Centres for Disease Control and Prevention (https://www.cdc.gov/)
- World Health Organisation (http://www.who.int/en/)
- National Institute on Alcohol Abuse and Alcoholism (https://www.niaaa.nih.gov/)
- International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/)
- Health evidence Canada (http://www.healthevidence.org/)
- U.S. Preventive Services Task Force (https://www.uspreventiveservicestaskforce.org/)
- Public Health England (https://www.gov.uk/government/organisations/public-health-england)
- Indigenous HealthInfoNet (http://www.healthinfonet.ecu.edu.au/)
- International Agency for Research on Cancer (https://www.iarc.fr/)
- World Cancer Research Fund (https://www.worldwidecancerresearch.org/)

Searches were not undertaken for unpublished literature.

Selection of the evidence

The titles and abstracts of records retrieved by the searches were screened for eligibility, with publications identified as being potentially relevant assessed in full text. These systematic reviews were assessed against the PEO criteria (specified in Table 1, Table 2, Table 3, and Table 4) for the overview in the first instance. These systematic reviews were also required to include cohort and/or case-control or case-crossover studies to be eligible. If other study types (e.g. cross-sectional studies) were included in the reviews, the results from the cohort and/or case-control studies had to be reported separately for the review to be included. They were then assessed against additional methodological quality criteria which are set out below. In addition, populations which are not judged to be relevant to the Australian context will be excluded (e.g. systematic reviews focused exclusively on African populations).

The titles and abstracts of the references retrieved from the searches were independently screened by one reviewer to identify studies that meet the eligibility criteria. Full-text copies of potentially relevant reviews were assessed by two reviewers to identify studies that satisfy the inclusion and exclusion criteria. Disagreements were resolved through discussion.

Additional criteria for considering reviews for inclusion

Step 1: Minimum criteria

Once a systematic review was identified as being eligible for inclusion, it was then assessed to see if it met a threshold for methodological quality. This was determined by considering selected methodological criteria from A Measurement Tool to Assess Systematic Reviews (AMSTAR) and Risk of Bias in Systematic Reviews (ROBIS) tools. These are tools for critically appraising the methodological quality (AMSTAR) and the risk of bias (ROBIS) of systematic reviews.

Systematic reviews were considered for inclusion in the overview if they met at least 2 of the following criteria:

1. **Comprehensive literature search (AMSTAR criteria 3{Shea, 2007 #291})**

To meet this criterion, the systematic review must have searched at least two electronic sources, specified the years and databases searched, and the key words and/or MESH terms. The searches should have been supplemented by checking the references in the primary studies identified.

2. **Characteristics of included studies in systematic reviews (AMSTAR criteria 6{Shea, 2007 #291})**

To meet this criterion, the systematic review should have specified (as a minimum): the age and gender of the participants, and any potential key confounders, such as tobacco use and co-morbidities. The systematic review should have also provided a clear and detailed description of the exposure, comparator(s), outcomes, and study type of the included primary studies.

3. **Quality assessment of included studies in systematic reviews (AMSTAR criteria 7{Shea, 2007 #291})**

To meet this criterion, the quality of each of the included studies needed to be reported in the systematic review using a pre-defined quality assessment tool appropriate for the study design.

4. **Inclusion and exclusion criteria (ROBIS Domain 1: study eligibility criteria{Whiting, 2016 #292})**

To meet this criterion, the systematic review should have clearly specified and provided an appropriate description and rationale for the inclusion and exclusion criteria for the population, exposure(s) and outcomes. Note that this is different from ROBIS Phase 1, which is about assessing the relevance of the inclusion and exclusion to the systematic review.

All systematic reviews assessed against these criteria were reported in the full-text screening tables provided in the Full Text Screening section. Note that some were given a 'partial' rating for a criterion. For example, for

quality assessment some systematic reviews did not assess study quality using a specific quality assessment tool but may have discussed and/or considered quality in a narrative way or in their analysis.

Step 2: Methods of analysis (ROBIS Domain 4: study eligibility criteria{Whiting, 2016 #292})

Any systematic reviews that met at least 2 of the criteria should have provided an adequate description of the methodology used to analyse the studies. If a meta-analysis was performed, the systematic review should have described and justified any subgroup or sensitivity analyses and methods used to deal with any heterogeneity.

This step involved two parts:

- The first was to assess whether the methods of analysis were sufficient to allow for reliable extraction and interpretation of the results. Many systematic reviews were excluded at this step. For example, systematic reviews that did not assess varying levels of alcohol consumption and only assessed a single exposure of 'any' alcohol consumption versus no alcohol consumption were excluded. Systematic reviews that included study design types other than cohort and/or case-control or case-crossover studies were only considered for inclusion if the results for the cohort and/or case-control or case-crossover studies were reported separately.
- Secondly, in the instance when two or more systematic reviews that met the minimum criteria and met the same number of criteria 1 to 4 then the methods of analysis was used to select the best quality review for inclusion. For example, the systematic review included for melanoma was selected over another systematic review based on its methods of analysis: it had a stratified analysis that included only studies that adjusted for sun exposure, which is a very important confounding variable for that outcome. Other systematic reviews may have been selected over other reviews because they considered other factors that may change the effect estimate like study design type and/or recall biases within their analyses.

Step 3: Date of search

When two or more systematic reviews that met the minimum criteria and met the same number of criteria 1 to 4 and they were both deemed to have the most appropriate methods of analysis at step 3, then the one with the most recent search date was selected for inclusion.

Reviews were excluded if:

1. They did not provide an adequate description of the methodology used to analyse the studies (any methodology, including narrative syntheses, maybe appropriate). The methods used were not appropriate or adequate justifications for methods of analysis were not provided. If a meta-analysis was performed the systematic review should describe and justify any subgroup or sensitivity analyses and methods to deal with any heterogeneity and study design type of included studies.
2. The study designs included in the systematic review were not case-control, cohort or case-crossover. Note that reviews were not excluded if they included other study design types (e.g. cross-sectional) and the results from the cohort and/or case-control studies were reported separately.
3. They were non-systematic reviews, primary studies, letters, editorials, animal studies, in-vitro studies, laboratory studies, conference abstracts and technical reports.
4. They were non-English language studies.
5. If they only focused on one type of alcoholic beverage, for example, beer or wine only.

Appraisal of individual eligible reviews

Levels of evidence

The NHMRC Evidence Hierarchy will be used to assess the level of evidence for each included study (see Table 6).

The review will aim to synthesise the highest level of evidence to answer the research question. As this is an overview of systematic reviews of an aetiological question the highest level of evidence is likely to be a systematic review of comparative cohort and/or case-control studies. A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies are of level II evidence (see Table 6).

Table 6: NHMRC evidence hierarchy: designations of 'levels of evidence' for intervention and aetiology research questions

Level	Intervention [a]	Aetiology [b]
I [c]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	A pseudorandomised controlled trial	All or none [d]
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial [e] • Cohort study • Case-control study • Interrupted time series with a control group	A retrospective cohort study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study [f] • Interrupted time series without a parallel control group	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

a. Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b).
b. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.
c. A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.
d. All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
e. This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).
f. Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

Quality assessment of the reviews

The quality of all included systematic reviews will be assessed by two independent reviewers using A Measurement Tool to Assess Systematic Reviews (AMSTAR). A copy of the tool is provided in Appendix 3. As

several items in this tool form part of the eligibility criteria for inclusion, all included reviews will score a minimum of 3.

Data extraction

Data was extracted from individual systematic reviews using a standardised data extraction form designed specifically for this overview. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies in data extraction were resolved by discussion or consultation with a third reviewer. Missing data from individual studies were not sought. See Appendix for the form.

Outcome definition and prioritisation

GRADE guidelines{Balshem, 2011 #19} specify that outcomes should be pre-specified and undergo an initial classification into three categories according to their importance for decision making (critical, important but not critical, or low importance) prior to undertaking the overview. The relative importance of the outcomes is to be reassessed after reviewing the evidence.

Classification of the importance of the outcomes was performed by the Alcohol Working Group prior to the start of review activities and confirmed as part of the GRADE process of interpreting the body of evidence identified in the overview.

The pre-specified outcomes to be included in the overview of the evidence on the health effects of alcohol consumption are presented in Table 7, Table 8, Table 9, and Table 10 with their importance as confirmed by the Alcohol Working Group.

Table 7: Outcomes to be included in the overview for short-term health effects (Question 1)

Outcome	Definition of outcome	Importance of the outcome
Injury to self (including physical and domestic violence, road traffic accidents, falls, fire / burns, occupational and drowning, self-harm and poisoning)	Harm or damage to body usually by an external force.	Critical for decision making
Acute cardiovascular events (including acute myocardial infarction, ischaemic stroke, haemorrhagic stroke and cardiac arrest, arrhythmia)	Recent onset disease that involves the heart or blood vessels.	Critical for decision making
Acute exacerbation of a mental illness	Acute exacerbation: a recent worsening of a medical disorder. Mental illness: Any of various disorders characterized by impairment of an individual's thoughts, emotions, or social functioning, including schizophrenia and mood disorders such as bipolar disorder.	Important, but not critical
Sexually transmitted infections (STI)	Diseases due to or propagated by sexual contact.	Important, but not critical
Harmful alcohol-drug interactions	The alteration of the intensity of the pharmacological effect of a drug by alcohol, so that the overall actions of the combination of alcohol plus drug are additive, potentiated, or antagonistic.	Important, but not critical
Sexual function	The constellation of mental aspects of sexuality - e.g., sexual arousal, sexual desire, sexual fantasies.	Important, but not critical
Acute GI (gastritis,	Recent onset symptom(s) of, relating to, or affecting the stomach and	Of limited importance

reflux)	intestines.	
Hangover	The disagreeable physical effects following excessive consumption of alcohol (or the use of other psychoactive drugs). Symptoms may include headache, fatigue, nausea, vomiting, and concentration difficulties.	Of limited importance

Table 8: Outcomes to be included in the overview for long-term health effects (Question 2)

Outcome	Definition of outcome	Importance of the outcome
All-cause mortality	All deaths reported in a given population.	Critical for decision making
All-cause morbidity	The proportion of patients with a particular disease during a given year per given unit of population.	Critical for decision making
All Cancers, including head and neck, breast, liver, colorectal, oesophageal, gastric, skin and prostate cancers.	A range of diseases in which some of the body's cells become defective, begin to multiply out of control, can invade and damage the area around them, and can also spread to other parts of the body to cause further damage.	Critical for decision making
Cardiovascular disease (CVD) including hypertension, stroke, cardiac failure, cardiomyopathy and arrhythmias.	Pathological conditions involving the cardiovascular system including the heart; the blood vessels; or the pericardium.	Critical for decision making
Liver disease including cirrhosis.	Any disease of the liver including cirrhosis which is a chronic degenerative disease in which normal liver cells are damaged and are then replaced by scar tissue.	Critical for decision making
Alcohol related pancreatitis.	Inflammation of the pancreas caused by consumption of alcohol.	Critical for decision making
Mental health disorders (depression, anxiety and alcohol-related psychosis).	Any of various disorders characterized by impairment of an individual's thoughts, emotions, or social functioning, including schizophrenia and mood disorders such as bipolar disorder.	Critical for decision making
Alcohol use disorders / dependence / withdrawal syndrome	Alcohol use disorder: a substance abuse disorder involving alcohol. Alcohol dependence: a condition characterised by a pathologic pattern of alcohol use causing a serious impairment in social or occupational functioning. Alcohol withdrawal syndrome: the clinical symptoms associated with cessation of alcohol consumption. These may include tremor, hallucinations, autonomic nervous system dysfunction, and seizures.	Critical for decision making
Diabetes and insulin resistance	Diabetes is a heterogeneous group of disorders characterized by hyperglycaemia and glucose intolerance. Insulin resistance is a diminished effectiveness of insulin in lowering blood sugar levels: requiring the use of 200 units or more of insulin per day to prevent hyperglycaemia or ketosis.	Critical for decision making
Thiamine deficiency	A nutritional condition produced by a deficiency of thiamine in the diet, characterized by anorexia, irritability, and weight loss. Later, patients experience weakness, peripheral neuropathy, headache, and tachycardia. In addition to being caused by a poor diet, thiamine deficiency in the United States most commonly occurs as a result of alcoholism, since ethanol interferes with thiamine absorption.	Critical for decision making
Quality of life	A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment; the overall condition of a human life.	Important, but not critical
Sleep disorders	Sleep disorders are a group of syndromes characterized by disturbance in the patient's amount of sleep, quality or timing of sleep, or in behaviours or physiological conditions associated with sleep.	Important, but not critical
Obesity/overweight	Overweight is a body mass index (BMI) of 25-29.9. Obesity is a BMI ≥30.	Important, but not critical
Peripheral neurological disorders	A disorder of the nerves outside of the brain and spinal cord.	Important, but not critical
Central neurological	Central neurological disorders are disorders of the brain and/or spinal cord.	Important, but not critical

disorders Seizures (co-morbidity) Cognitive impairment / dementia including Korsakoff's syndrome.	Seizures are uncontrolled electrical activity in the brain, which may produce a physical convulsion or fit, minor physical signs, thought disturbances, or a combination of symptoms.[***] Cognitive impairment refers to disturbances in the mental process related to thinking, reasoning, and judgment. Dementia refers to the impairment of brain function, involving memory, thinking and concentration. 14 Korsakoff's syndrome is a memory disorder which is caused by a deficiency of vitamin B1, also called thiamine.	
Fertility	The capacity to conceive or to induce conception. It may refer to either the male or female.	Important, but not critical
Osteoporosis (+/- fracture, bone healing)	Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis (osteoporosis, postmenopausal) and age-related or senile osteoporosis.	Of limited importance
Gout	Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi.	Of limited importance
Reflux	Gastrointestinal reflux disease resulting from reflux of stomach contents into the oesophagus. Major symptoms are heartburn, indigestion and regurgitation.	Of limited importance
Respiratory diseases	Disorders of the respiratory system including trachea and lungs.	Of limited importance
Hormonal disorders	Disorders of the endocrine system.	Critical for decision making

Table 9: Outcomes to be included in the overview for alcohol consumption in pregnant women (Question 3)

Outcome	Definition of outcome	Importance of outcome
Fetal alcohol spectrum disorder (FASD)	The diagnosis of FASD is complex and ideally requires a multidisciplinary team of clinicians to evaluate individuals for confirmation of alcohol exposure during pregnancy and neurodevelopmental problems (impairments to development of brain and central nervous system) and facial abnormalities in the context of a general physical and developmental assessment. Currently the diagnosis of FASD can be divided into one of two sub-categories: 1. FASD with three sentinel facial features (similar to the previous category of Fetal Alcohol Syndrome without a requirement for growth impairment) 2. FASD with less than three sentinel facial features (which encompasses the previous Partial Fetal Alcohol Syndrome and Neurodevelopmental Disorder-Alcohol Exposed category).	Critical for decision making
Low birth weight	Baby born weighing less than 2.5kg.	Critical for decision making
Small for gestational age	Weighing below the 10th percentile for gestational age.	Critical for decision making
Developmental delay	When a young child is slower to develop physical, emotional, social and communication skills than is expected in children of that age.	Critical for decision making
Birth defects	A baby born with a part of the body missing or malformed.	Critical for decision making
Stillbirth	The event that a fetus is born dead or stillborn.	Critical for decision making
Behavioural problem	Troublesome or disruptive behavioural displays.	Critical for decision making
Neonatal withdrawal	Fetal and neonatal addiction and withdrawal as a result of the mother's dependence on drugs (in this case alcohol) during pregnancy. Withdrawal or abstinence symptoms develop shortly after birth. Symptoms exhibited are loud, high-pitched crying, sweating, yawning and gastrointestinal disturbances.	Important, but not critical
Premature birth	Childbirth before 37 weeks of pregnancy (259 days from the first day of the mother's last menstrual period, or 245 days after fertilisation).	Important, but not critical
Spontaneous abortion and miscarriage	Expulsion of the product of fertilisation before completing the term of gestation and without deliberate interference.	Important, but not critical

Table 10: Outcomes to be included in the overview for alcohol consumption in breastfeeding women (Question 4)

Outcome	Definition of outcome	Importance of outcome
Cognitive impairment	Disturbances in mental processes related to learning, thinking, reasoning, and judgment.	Critical for decision making
Sudden infant death syndrome (SIDS)	The abrupt and unexplained death of an apparently healthy infant under one year of age, remaining unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.	Critical for decision making
Sedation (concentration in breast milk)	Reduction of anxiety, stress, irritability, or excitement by administration of a sedative agent or drug (in this case alcohol in breast milk).	Critical for decision making
Child neglect/bonding	Child neglect is the failure by parents or guardians to provide for the basic human needs of a child by physical or emotional deprivation that interferes with normal growth and development or that places the child in jeopardy Bond is the emotional and physical attachment occurring between a parent or parent figure, especially a mother, and offspring, that usually begins at birth and is the basis for further emotional affiliation.	Critical for decision making
Failure to thrive	A condition of substandard growth or diminished capacity to maintain normal function.[13]	Important, but not critical

Assessment of the body of evidence

Overview of GRADE

The Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach was used to guide assessment of the underlying evidence presented in the systematic reviews{Balshem, 2011 #19}.

The evidence for each outcome was assessed using the GRADE system for rating the quality of evidence{Balshem, 2011 #19} with some modification for the assessment of a public health intervention{Harder, 2015 #16}. Under the GRADE system, the overall quality of the evidence for an outcome is categorised as high, moderate, low or very low. On the advice of the NHMRC, and with the approval of the Alcohol Working Committee, this review has adopted the GRADE categorisation suggested by Harder et al (2015){Harder, 2015 #16}, in which evidence from randomised controlled trials is initially graded as high quality and evidence from observational studies is initially graded as low quality. As the most appropriate study type to answer the research questions are systematic reviews of prospective observational studies, we will rate prospective observational studies at low risk of bias initially as 'moderate' as opposed to 'low'{Harder, 2015 #16}.

The GRADE approach is per outcome there is no process within GRADE to synthesise the results across multiple systematic reviews or to estimate effect size for the body of evidence. To date GRADE has been infrequently applied to overviews and there is currently no guidance on how to apply GRADE to overviews; however a project to develop GRADE methods for overviews of systematic reviews is currently being undertaken.

Only information reported in the systematic reviews were used to inform this assessment, primary studies were not retrieved or reviewed.

The quality of the evidence can be decreased by 1 or 2 if any of the following conditions are met.

Factor	Consequence
Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 level

The quality of the evidence, described in further detail below, can be increased if any of the following conditions are met.

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

It should be noted that GRADE does not recommend upgrading when downgrading has occurred. However, it was agreed that for the purpose of this overview, in order to differentiate greater between the levels of evidence, we have upgraded when downgrading has occurred.

GRADE domain 1: Limitations in study design or execution (risk of bias)

This domain in GRADE refers to limitations that may bias the effect estimate.

For observational studies, GRADE highlights a number of potential limitations (in the table below); however additional limitations may be present.

Table 11: Potential limitations of observational studies

Potential limitation	Example
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	Under- or over-matching in case-control studies Selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	Differences in measurement of exposure (e.g. recall bias in case-control studies) Differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	Failure of accurate measurement of all known prognostic factors Failure to match for prognostic factors and/or adjustment in statistical analysis
Incomplete or inadequately short follow-up	Especially within prospective cohort studies, both groups should be followed for the same amount of time.

As noted in the table above, failure to adequately control confounding may increase bias. Many of the included studies in the identified systematic reviews did not adjust for confounding variables, and when they did, the factors adjusted for ranged from age and sex only to fully adjusted models. Consequently, this reduces the confidence of the results in these studies, and any corresponding meta-analysis, as there may be residual confounding present.

Not all included systematic reviews assessed the risk of bias in the primary studies. In those which did, the assessments were often poorly reported and insufficient for reliable interpretation and assessment of the methodological quality of the review and its included studies. This is compounded by the poor reporting of the included studies. Many of the included systematic reviews also commented on the poor methodological quality of the included studies and the differences that study design and recall biases may have on the observed effect sizes reported. Additionally, many of the included reviews did not meet all the criteria set in the protocol and only met the minimum criteria for inclusion in the overview (2 out of the 4 additional criteria).

Prospective cohort studies are considered in the NHMRC Evidence Hierarchy (Table 6) to be a higher level of evidence than case-control studies for aetiological research questions. Many of the systematic reviews identified included both cohort studies and case-control studies, which were often meta-analysed together. As case-control studies are susceptible to the introduction of more bias than prospective cohort studies, we are less confident in the results from a systematic review that combines both study types in its meta-analysis is than from a systematic review which includes only prospective cohort studies. Additionally, some systematic reviews did report study types separately and found differences in the observed effect sizes dependent on study types.

However, upon agreement with the NHMRC and AWC, we downgraded by 1, instead of by 2, if the systematic review did not assess risk of bias but only included prospective cohort studies or had less than 25% of the population from case-control studies. If the systematic review did perform quality assessment and determined the risk of bias to be low but the systematic review included case-control studies we have downgraded by 1, due to the higher risk of bias in a case-control study design.

While we have considered the quality of systematic reviews in our inclusion and exclusion criteria in the systematic reviews and have conducted AMSTAR assessments on these, we have only considered the risk of bias in the primary studies for the GRADE assessment. The quality of the included systematic reviews ranged from 2 to 9 (out of 11) on the AMSTAR checklist. It should be noted that the AMSTAR checklist itself may not

accurately reflect the quality of the included studies and it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in peer reviewed publications.

Please refer to the summary of findings table footnotes for each outcome for explanations on reasons for downgrading for that particular outcome.

GRADE domain 2: Inconsistency of results

Inconsistency in GRADE refers to an unexplained heterogeneity of results. We downgraded by 1 or 2 depending on the level of heterogeneity present, if any was detected. GRADE guidance suggests the following for heterogeneity using the I2 statistic: 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity, and 75%-100% is considerable heterogeneity. The highest level of heterogeneity detected was used. If one subgroup for an outcome had considerable heterogeneity then it was downgraded by 2 even if other subgroups had low or moderate heterogeneity. If heterogeneity was detected but sufficiently explored and explained through subgroup/sensitivity analysis and the systematic review reported these results then the systematic review was not downgraded for heterogeneity.

We did not consider consistency across primary studies in the direction of effect. We have referred to consistency across systematic reviews that met the minimum criteria for inclusion for that outcome, but we did not include this assessment as part of the GRADE process, due to the selection of only one systematic review for inclusion.

Significant heterogeneity was observed in most of the included studies which decreases our confidence in the results. While heterogeneity was often explored through sensitivity or subgroup analysis the analyses undertaken was often insufficient and all potential sources of heterogeneity were not fully explored. This is a limitation of the overview approach as it relies on the reporting of the pooled analyses from the systematic reviews and the analyses to explore any heterogeneity that were carried out by the review authors. In some of the included studies there were additional analyses that could have been carried out by the systematic reviews that may or may not have explained the heterogeneity observed.

Please refer to the summary of findings table footnotes for each outcome for explanations on reasons for downgrading for that particular outcome.

GRADE domain 3: Indirectness of evidence

Indirectness in GRADE refers to indirectness in the population, exposure or outcome, when comparing the systematic reviews PEO to the PEO of this overview. We downgraded if there was indirectness in the population, due to potential residual confounding that may affect the results. We did not downgrade if an outcome included both incidence and mortality as outcomes because the outcomes in the protocol did not specify incidence or mortality for outcomes.

Please refer to the summary of findings table footnotes for each outcome for explanations on reasons for downgrading for that particular outcome.

GRADE domain 4: Imprecision

GRADE recommends that the boundaries of the confidence intervals of the estimate of effect are used for assessing imprecision. This can be done by agreeing in advance with the committee minimal important differences (MIDs), or using default MIDs. MIDs were not set in advance with the AWC or NHMRC and we did not use the default MIDs. This is because the effect sizes for alcohol are usually dose-dependent and the MIDs are likely to vary widely between outcomes; therefore applying a default MID would not be appropriate.

Please refer to the summary of findings table footnotes for each outcome for explanations on reasons for downgrading for that particular outcome.

GRADE domain 5: Publication bias

As per the GRADE handbook "Publication bias is a systematic under-estimation or an over-estimation of the underlying beneficial or harmful effect due to the selective publication of studies. Confidence in the combined estimates of effects from a systematic review can be reduced when publication bias is suspected, even when the included studies themselves have a low risk of bias."

For assessing publication bias in GRADE, we downgraded by 1 if the systematic review authors detected publication bias. If the systematic review did not assess publication bias then we also downgraded this by 1 as the possibility of publication bias occurring is unknown. We also considered publication bias likely if the systematic review only search one database, unless this was justified by the systematic review authors.

Please refer to the summary of findings table footnotes for each outcome for explanations on reasons for downgrading for that particular outcome.

Development of evidence summaries

Evidence summaries for each outcome were developed. The evidence summaries are independent of the GRADE process and do not take into account the certainty and strength of the evidence. For the certainty and strength of the evidence please refer to the summary of findings table for each outcome.

Each evidence summary includes a summary of the results of the selected systematic review for that outcome, including the direction of effect.

If a dose-response analysis was conducted in the systematic review, then the dose-response association is referred to in the evidence summary. If a dose-response analysis was not undertaken, then the dose-response association is not known and a categorical level will instead be indicated.

The reference groups may consist of occasional drinkers, lifetime abstainers or current abstainers, which may include former drinkers, all of whom are variously defined and some of whom may carry excess risk. The evidence summary states what the reference groups consisted of, when this was reported in the systematic review, if it was not reported in the systematic review then it was not possible to add this information to the evidence summary. It should also be noted that the reference group in the included systematic review can vary between the primary studies. For example, for the studies that reported a J-shaped association particularly, there was discussion in some systematic reviews around the reference categories and the potential for abstainer bias, such as in Stockwell 2016{Stockwell, 2016 #6737}.

The evidence summary states if the effect size was large, determined by whether or not it was upgraded in GRADE for a large effect size. It also notes if the effect size was small.

Whether or not the selected systematic review results is similar to the results of the other systematic reviews identified for that outcome that met the minimum criteria is referred to. If there is no mention of this within an evidence summary then this is because no other systematic reviews were identified for that outcome that met the minimum criteria.

Selecting one systematic review per outcome

Multiple systematic reviews identified for one outcome, and the corresponding overlap and gaps in included primary studies, is a common problem encountered by overviews and may result in a number of potential problems{Ballard, 2017 #23}. For example, if results from different meta-analysis are pooled and overlaps in primary studies included in the meta-analysis are not accounted for, then this may result in an inaccurate overestimate of the results{Pieper, 2014 #24;Smith, 2011 #25}. There is currently a lack of guidance on how to deal with the overlapping studies within overviews{Group, 2012 #26}.

One method of dealing with the problem of overlapping systematic reviews is to select only one systematic review for inclusion when multiple systematic reviews are identified for an outcome{Group, 2012 #26}. This overview of reviews has selected only one systematic review for inclusion for each outcome, based on currency and quality.

For some outcomes there were multiple systematic reviews that meet the minimum criteria for inclusion in the overview and included some of the same primary studies but not others. We have been clear in the 'Full text screening document' about how we chose the systematic review and have included the one with the most recent search date where possible. However, in the instance that there is another systematic review, with similar search dates, that also meets the minimum criteria, we have referred to this systematic review and its results in the evidence evaluation. We have not included a full summary of findings table or conducted an AMSTAR assessment or any data extraction for that systematic review. However, a summary of the results and the author's conclusions are available in the technical report and are referred to in the evidence evaluation.

Risk of bias in systematic reviews

Although systematic reviews are considered to provide a high-level of evidence, they are, like other study types, susceptible to biases, poor conduct, misleading conclusions, and poor reporting and the increasing number of published systematic reviews has increased the frequency of these problems{Ioannidis, 2016 #6}. There is currently a lack of guidance on how to deal with the low quality of systematic reviews in overviews{Pieper, 2014 #24}.

In order to reduce this risk, this protocol took the approach of only including systematic reviews which meet stringent criteria for quality, relevance and currency. Unfortunately, most identified systematic reviews did not meet the minimum criteria set in the protocol and these criteria had to be lowered for most outcomes.

The quality of reporting of the included systematic reviews ranged from 2 to 9 (out of 11) on the AMSTAR checklist. It should be noted that the AMSTAR checklist itself may not accurately reflect the quality of the included studies and it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in peer reviewed publications.

The poor quality of many of the included systematic reviews limits our confidence in the overview findings. This is compounded by the poor quality of the included studies.

Risk of bias in primary studies

One of the criteria that were frequently not met by the systematic reviews reviewed at full text was conducting risk of bias assessment of the primary studies. The approach suggested in these circumstances is for the overview authors to assess the primary studies; however this was not possible due to contractual and time constraints{Higgins, 2011 #11}. The other method is to restrict the included studies to only those that conduct a risk of bias assessment{Caird, 2015 #27}. Unfortunately, there were such a small proportion of systematic reviews that actually conducted a risk of bias assessment that following this approach and would have resulted in very few reviews being included in the overview. Therefore, it was decided to include reviews that did not assess risk of bias. This is a common problem experienced by overview authors: Hartling et al., 2012 noted that only <40% of overviews extract the quality of primary studies included in the systematic reviews.

In those systematic reviews which did assess risk of bias of primary studies, the assessments were often poorly reported and insufficient for reliable interpretation of the review and its included studies. Many of the included systematic reviews also commented on the poor methodological quality of the included studies and the differences that study design and recall biases may have on the observed effect sizes reported.

Data extraction and AMSTAR assessment

Data was extracted from individual systematic reviews using a standardised data extraction form designed specifically for this overview. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies in data extraction were resolved by discussion or consultation with a third reviewer. Missing data from individual studies were not sought.

Anstey 2009

Table 12: Data extraction for Anstey 2009

General information	Systematic Review	Yes
	Title	Alcohol Consumption as a Risk Factor for Dementia and Cognitive Decline: Meta-Analysis of Prospective Studies
	Country of origin	SR: Australia
	Source of funding	This work was supported by Dementia Collaborative Research Centres, Can Australian Government Initiative (to HAM), NHMRC Research Fellowship No. 366756 (to KJA), Alzheimer's Australia Research and the Centre for Mental Health Research at the Australian National University (to NC).
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	The relationships between alcohol consumption and dementia and cognitive decline
	Search Methods	PubMed (1950 to June 2007), PsycINFO (1872 to June 2007), and the Cochrane Library (1800 to June 2007), with searches being limited to studies in English and focused on humans. The reference lists of the retrieved articles were also hand searched for other applicable publications. The alcohol terms included ethanol, alcohol, alcohol*, drink*, drunk, drunk* (drunkenness), blood alcohol concentration/content, blood alcohol level, substance use/misuse/abuse/addiction, substance dependence/dependent, substance user(s), substance disorder(s), substance-related disorder(s), substance usage, substance abuser(s), substance addict(s), intoxicated, intoxication, abstinence, abstinent, abstainer(s), sober, sobriety, liquor, spirits, beer, ale, wine, brandy, gin, rum, tequila, vodka, whiskey/whisky, and champagne. The dementia and cognition terms included cognit*, cognitive, cognition, intell*, IQ, memory, Mini-Mental State Examination, Mini Mental Status Examination, dement* (dementia(s), demented, nondemented), VaD, Alzheimer*, senil*, presenil*, presenil*, mild cognitive impairment, mild cognitive impairment (MCI), neurocognit*, neurocognition, neurocognitive, neuropsychological assessment(s)/test(s)/testing/evaluation(s)/ exam(s)/examination(s)/measure(s)/ measurement(s), general mental ability, attention, executive function*, executive process*, executive process, executive control, psychomotor, perceptual speed, perceptual motor, reaction time, processing speed, speed of processing, crystallized intelligence#, crystallized ability#, fluid intelligence, and fluid ability.
	Level of evidence (lowest identified)	Level II
	Study types identified	Prospective cohort studies
	Quality of evidence evaluated and summary of RoB	NR - prospective cohort studies only
	RoB tool used	NR

	Inclusion criteria	Minimum follow-up period of 1 year Outcome measures had to include either dementia or cognitive decline. Screened for dementia at baseline or adjusted for cognitive function in the analyses. Studies evaluating cognitive change were required to have measured cognition at both baseline and follow-up periods and either implemented a dementia assessment at baseline, which excluded those participants with cognitive impairment or dementia, or adjusted for incident dementia and/or baseline cognition performance in analyses. Measure exposure to alcohol at baseline or during a follow-up period that preceded the final follow-up examination
	Exclusion criteria	Experimental and clinical studies (alcoholics compared with controls)
Exposure	Definition	Alcohol consumption
	Method of measurement	measure exposure to alcohol at baseline or during a follow-up period that preceded the final follow-up examination
	Reference category	Non-drinkers (not confined to lifetime abstainers)
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	AD, VaD, Any dementia, cognitive performance, MCI, or cognitive impairment
	Method of measurement	NR
	No. of studies and participants analysed by type of study	14 prospective cohort studies
	No. of studies and participants excluded or missing (with reasons) by type of study	32,825 studies excluded at title/abstract screen 124 did not meet the inclusion criteria at full text screen 22 publications on duplicate cohort 5 irrelevant/unusable data 10 data insufficient for meta-analysis
	Statistical method of analysis	OR, RR, HR all analysed together.
	Significance/direction	Moderate alcohol consumption in older adults is associated with reduced risk of dementia.
	Heterogeneity	The test for heterogeneity was significant for AD (X2=11.43, p = 0.04).
	Results	The meta-analysis reported that light to moderate drinking (ranges included 1-21, 1-27, 2-28, 1-14 or unspecified units per week) was a protective factor compared to non-drinking. For Alzheimer's disease pooled RR = 0.72 (95% CI 0.61-0.87). For Vascular dementia pooled RR = 0.75 (95% CI 0.57-0.98). For any dementia pooled RR = 0.74 (95% CI 0.61-0.91). The meta-analysis comparing heavy alcohol consumption to not drinking reported no significant differences. Five articles recorded information on former drinkers compared with lifetime abstainers. – Three studies found no differences - One study found that when former drinkers were excluded from the non-drinker group, the effect sizes of the study reduced. - Another study found that former drinkers had 20%–60% higher odds of incident dementia than abstainers.
Authors' conclusion	We conclude that light to moderate alcohol consumption in older adults is associated with reduced risk of dementia.	
Reviewer's notes	Note: OR, RR, HR all analysed together. Prospective only. All studies adjusted for age and sex in their analyses.	

Table 13: AMSTAR assessment for Anstey 2009

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	

6	Were the characteristics of the included studies provided? [f]	No	Confounders not stated
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	No	
11	Was the conflict of interest stated? [k]	No	Not stated for review or included study authors

Bagnardi 2015

Table 14: Data extraction for Bagnardi 2015

General information	Systematic Review	Yes
	Title	Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis
	Country of origin	Italy
	Source of funding	Italian Association of Cancer Research
	Possible conflicts of interest (for study authors or translators)	Authors declare no conflicts of interest
AMSTAR Rating		2/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	to provide a more global picture of the association between alcohol drinking and a large variety of cancers
	Search Methods	MEDLINE, ISI Web of Science and EMBASE using MeSH headings and free text. Hand search of relevant studies. Search period: to September 2012
	Level of evidence (lowest identified)	III-3
	Study types identified	Cohort and case-control
	Quality of evidence evaluated and summary of RoB	Not reported. Sensitivity analysis by study type (cohort vs case-control) where more than 10 studies were identified for a specific cancer site.
	RoB tool used	None
	Inclusion criteria	1. Case-control, cohort or nested case-control published as original articles 2. Studies that reported findings as odds ratio, relative risk or hazard ratio for at least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers 3. Studies that reported standard errors or confidence intervals of the risk estimates or provided sufficient data to calculate them
	Exclusion criteria	Studies reporting on specific type of alcoholic beverages only (e.g. beer only)
Exposure	Definition	Light (≤12.5g per day), moderate (≤50g per day) and heavy (>50g per day) drinking
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	Non and/or occasional drinkers (sensitivity analysis excluding occasional drinkers)
	Statistical approach	Used method of Hamling (2008)
Results: (Brain cancer)	Definition of outcome	Incidence or mortality of brain cancer
	Method of measurement	NR
	No. of studies and participants analysed by type of study	4 cohort, 2 case-control studies (1,808 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None excluded from meta-analysis
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Non-significant, no effect
	Heterogeneity	I^2=6% (light), 58% (moderate) and 42% (heavy)
	Results	RR 1.01 (0.86-1.18) light, 1.10 (0.84-1.43) moderate, 1.45 (0.69-3.08) heavy
Results: (Cervical cancer)	Definition of outcome	Incidence or mortality of cervical cancer
	Method of measurement	NR
	No. of studies and participants analysed by type of study	2 cohort, 3 case-control studies (1,588 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None excluded from meta-analysis
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis

General information	Systematic Review	Yes
		using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Non-significant, no effect
	Heterogeneity	I^2=0% (light), 7% (moderate)
	Results	RR 0.87 (0.75-1.01) light, 0.90 (0.73-1.11) moderate, Not evaluable for heavy consumption.
Results: (Hodgkin's lymphoma)	Definition of outcome	Incidence or mortality of Hodgkin's lymphoma
	Method of measurement	NR
	No. of studies and participants analysed by type of study	2 cohort, 7 case-control studies (1,335 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None excluded from meta-analysis
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Significant, decreased risk
	Heterogeneity	I^2=6% (light), 0% (moderate), 0% (heavy)
	Results	RR 0.73 (0.59−0.89) light, 0.73 (0.60−0.87) moderate, 0.63 (0.41−0.97) heavy consumption.
Results: (Lung cancer)	Definition of outcome	Incidence or mortality of lung cancer
	Method of measurement	NR
	No. of studies and participants analysed by type of study	18 cohort, 16 case-control studies (38,423 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None excluded from meta-analysis
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Non-significant, no effect
	Heterogeneity	I^2=44% (light),57% (moderate), 73% (heavy)
	Results	RR 0.84 (0.79−0.88) light, 0.98 (0.92−1.05) moderate, 1.15 (1.02−1.30) for heavy consumption. As drinking and smoking are strongly associated, residual confounding by smoking might have biased this result.
Results: (Mouth, pharynx and larynx cancer)	Definition of outcome	Incidence or mortality of oral cavity and pharynx, larynx
	Method of measurement	NR
	No. of studies and participants analysed by type of study	Mouth and pharynx: 5 cohort, 47 case-control studies (13,895 cases) Larynx: 3 cohort, 38 case-control (7,059 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None excluded from meta-analysis
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Significant, positive association
	Heterogeneity	Mouth and pharynx: I^2=26% (light),72% (moderate), 77% (heavy) Larynx: I^2=39% (light), 61% (moderate), 77% (heavy)
	Results	Mouth and pharynx: RR 1.13 (1.00−1.26) light, 1.83 (1.62−2.07) moderate, 5.13 (4.31−6.10) for heavy consumption. Larynx: RR 0.87 (0.68−1.11) light, 1.44 (1.25−1.66) moderate, 2.65 (2.19−3.19) for heavy consumption.
Results: (non-Hodgkin's lymphoma)	Definition of outcome	Incidence or mortality of non-Hodgkin's lymphoma
	Method of measurement	NR
	No. of studies and participants analysed by type of study	9 cohort, 15 case-control studies (14,124 cases)
	No. of studies and participants	None excluded from meta-analysis

General information	Systematic Review	Yes
	excluded or missing (with reasons) by type of study	
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. Dose-risk analysis using a random effect meta-regression based on a nonlinear dose-response relationship framework.
	Significance/direction	Significant, decreased risk
	Heterogeneity	I^2=65% (light), 35% (moderate), 10% (heavy)
	Results	RR 0.88 (0.80−0.97) light, 0.87 (0.81−0.95) moderate, 0.75 (0.64−0.88) heavy consumption.
Authors' conclusion	Alcohol was not significantly associated with the risk of brain cancer Alcohol was not significantly associated with the risk of cervical cancer Alcohol was significantly associated with a decreased risk of Hodgkin's lymphoma Heavy consumption was significantly associated with the risk of lung cancer but this may be biased by residual confounding. Every category of alcohol consumption, from light to heavy drinking, was associated with an increased risk of cancer – in a dose–risk manner – of oral cavity and pharynx Moderate and heavy drinking, but not light drinking, was associated with an increased risk of cancer of larynx Alcohol was significantly associated with a decreased risk of non-Hodgkin's lymphoma	
Reviewer's notes		

Table 15: AMSTAR assessment for Bagnardi 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	List of included studies was provided
6	Were the characteristics of the included studies provided? [f]	No	Only in aggregated form (note that the review includes 572 studies)
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	Sub-group analysis of cohort and case-control studies partially addresses this
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	No	
11	Was the conflict of interest stated? [k]	No	

Bay 2011

Table 16: Data extraction for Bay 2011

General information	Systematic Review	Yes
	Title	Prenatal alcohol exposure – a systematic review of the effects on child motor function
	Country of origin	SR: Denmark
	Source of funding	No specific funding.
	Possible conflicts of interest (for study authors or translators)	The authors have stated explicitly that there are no conflicts of interest in connection with this article.
AMSTAR Rating		4
Characteristics of review and included primary studies	Aim/objectives of systematic review	To systematically review the available evidence on the effects of prenatal alcohol exposure on motor function in humans.
	Search Methods	17 February 2010 using Medline, Embase, Web of Science, Scopus and The

		Cochrane Library. The MeSH headings alcohol, alcohol drinking, alcohol-related disorders, pregnancy, motor skills, motor skills disorders, and child development were combined in all relevant ways. Free text terms alcohol, pregnancy and motor
	Level of evidence (lowest identified)	Level IV
	Study types identified	Follow-up or case-control studies
	Quality of evidence evaluated and summary of RoB	The quality of the studies was assessed using the Newcastle–Ottawa Quality Assessment Scale, and many studies were generally of high quality but differed in some substantial ways. No score for each of the included studies was reported.
	RoB tool used	Newcastle–Ottawa Quality Assessment Scale
	Inclusion criteria	Published in peer-reviewed journals in the English language
	Exclusion criteria	Case series, case reports and reviews If the children's motor functions had not been evaluated and scored on a standardized or validated test Duplicate publication
Exposure	Definition	Levels of alcohol consumption
	Method of measurement	Exposure group with 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.
	Reference category	Abstainers or very low consumers (varied between included studies)
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	Child motor function
	Method of measurement	NR (included studies used various different scales and measures)
	No. of studies and participants analysed by type of study	23 studies included
	No. of studies and participants excluded or missing (with reasons) by type of study	256 not relevant
	Statistical method of analysis	Narratively reported. Four out of six studies for moderate-high daily intake (3–5 drinks/day) reported no significant association for risk of child motor development compared to no alcohol (2 studies), <1.5oz/day (1 study) and no alcohol plus a level of alcohol consumption that was not reported outside the hospital (one study). One other study reported gross and fine motor skill deficiencies at in infants of 13 months age whose mothers consuming an average of 4.7drinks/day compared to not drinking during pregnancy. The remaining study reported deficiencies in motor performance in infants aged 3 days, abnormal reflexes in 30 day-olds and gross and fine motor skills in 6 month-olds whose mothers consumed an average of 4.2 drinks/day compared to not drinking during pregnancy. Seven out of 13 studies on low alcohol consumption (1–2 drinks/day) reported significant effects on child motor development of maternal alcohol consumption>10 drinks/week when compared to not drinking (6 studies) or <0.1oz/day alcohol consumption (1 study) during pregnancy. Six out of 13 studies reported an increased risk for low alcohol consumption (1–2 drinks/day) on fine motor functions compared to not drinking (5 studies) or <0.1oz/day alcohol consumption (1 study) during pregnancy. Four out of 13 studies on low alcohol consumption (1–2 drinks/day) reported poorer performances of gross motor skills compared to not drinking (3 studies) or <0.1oz/day alcohol consumption (1 study) during pregnancy. For low-moderate exposure (1–7 drinks/week) there was no difference reported on child motor development.
	Significance/direction	The risk of poorer child motor function may increase with higher levels of alcohol consumption.

	Heterogeneity	Because of the heterogeneity of the studies (no value reported) meta-analysis was deemed not appropriate.
	Results	Not extracted for drinking versus not drinking or for binge drinking versus not binge drinking (where the alcohol consumption level of the reference group was
Authors' conclusion	While it appears consistent that high daily alcohol intake is associated with deficits in gross and fine motor function, and low weekly intake is not associated with such deficits, the issue of binge drinking is unsettled.	
Reviewer's notes		

Table 17: AMSTAR assessment for Bay 2011

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]		
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies list not provided.
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	The NOS score for the individual studies was not reported.
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	No meta-analyses but justified.
10	Was the likelihood of publication bias assessed? [j]	No	
11	Was the conflict of interest stated? [k]	No	

Berg 2008

Table 18: Data extraction for Berg 2008

General information	Systematic Review	Yes
	Title	Association Between Alcohol Consumption and Both Osteoporotic Fracture and Bone Density
	Country of origin	SR: USA
	Source of funding	Program of Research Integrating Substance Use in Mainstream Healthcare with support from the Robert Wood Johnson Foundation, National Institute on Drug Abuse (NIDA), and National Institute on Alcohol Abuse and Alcoholism (co-directors A. T. McLellan, PhD, and B. J. Turner, MD, MSEd). Additional support was provided by grants K23 DA021087 from the NIDA and the National Institute of Mental Health and a Robert Wood Johnson Foundation Physician Faculty Scholar Award to Dr Berg; grants R25 DA14551 and R01 DA015302 from the NIDA to Dr Arnsten; and a Center for AIDS Research grant (P30 AI51519) to the Albert Einstein College of Medicine of Yeshiva University from the National Institutes of Health.
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		7
Characteristics of review and included primary studies	Aim/objectives of systematic review	Alcoholism is a risk factor for osteoporotic fractures and low bone density, but the effects of moderate alcohol consumption on bone are unknown. We performed a systematic review and meta-analysis to assess the associations between alcohol consumption and osteoporotic fractures, bone density and bone density loss over time, bone response to estrogen replacement, and bone remodelling.

	Search Methods	May 14, 2007 Cochrane Central Register of Controlled Trials, Current Contents Connect, and PsychINFO. Manually searched references of included studies and pertinent reviews. MeSH Terms: Alcohol-related disorders, Alcoholism, Alcoholic beverages, Alcohol drinking, Osteoporosis, Postmenopausal osteoporosis, Bone density, Metabolic bone diseases, Pathologic bone demineralization, Fractures, Spontaneous fractures, Hip fracture, Spinal fractures, Wrist injuries, Bone resorption Text Words: Alcohol, alcoholic, alcoholism, beer, wine, liquor, Osteoporosis, osteopenia, bone mineral density, BMD, bone resorption, Compression fracture, fragility fracture, atraumatic fracture, Telopeptide, n-telopeptide, c-telopeptide, osteocalcin, bone-Gla protein, BGP, bone and alkaline phosphatase, deoxypyridinoline, hydroxyproline, tartrate-resistant acid phosphatase, TRACP, bone and sialoprotein, hydroxylysine
	Level of evidence (lowest identified)	Level IV
	Study types identified	Cohort Case-control
	Quality of evidence evaluated and summary of RoB	Fair
	RoB tool used	Internal validity criteria of the US Preventive Services Task Force,20 assigning a rating of "good" when all criteria were met, "fair" when 1 or more criterion was partially met and the study contained no fatal flaws, and "poor" if 1 or more criterion was not met
	Inclusion criteria	Experimental, cohort, or case-control designs; included adults both exposed and not exposed to alcohol; and reported on at least 1 outcome.
	Exclusion criteria	Alcohol consumption and bone density were measured once at the same point in time to avoid invalid assumptions about temporal sequence.
Exposure	Definition	adults exposed to alcohol
	Method of measurement	studies reported alcohol consumption using numerous units of measurement, we converted alcohol consumption into drinks per day by estimating that each standard drink is equivalent to 14 g or 0.6 fluid oz. of pure alcohol, that there are 29 kJ/g of alcohol, and that 1 unit of alcohol equals 8 g of pure alcohol.
	Reference category	adults not exposed to alcohol
	Statistical approach	studies were rated "good" if alcohol consumption was reported as a rate (e.g., "drinks per day") and reflected data from more than a single survey item (i.e., from separate questions about consumption of beer, wine, or spirits). Studies that used a single survey item, or did not sufficiently explain their measures, were rated "fair." Studies that used imprecise definitions of alcohol consumption (e.g., "ever," "daily," or "yes") were rated "poor."
Results: (per outcome)	Definition of outcome	Hip fracture
	Method of measurement	Diagnosis of fracture
	No. of studies and participants analysed by type of study	13 studies 8 cohort, 5 case-control
	No. of studies and participants excluded or missing (with reasons) by type of study	764 studies excluded at title/abstract screen 117 studies were rated as "poor" and excluded
	Statistical method of analysis	Combined fracture data by log transforming reported effects in each stratum and then pooled data with the random effects models.
	Significance/direction	Benefit at lower levels of consumption
	Heterogeneity	None detected
	Results	Compared with abstainers, persons consuming from more than 0.5 to 1.0 drinks per day had lower hip fracture risk (RR=0.80 [95% confidence interval, 0.71-0.91]), and persons consuming more than 2 drinks per day had higher risk (relative risk 1.39 [95% confidence interval, 1.08-1.79]). >1 to 2 drinks RR=0.91 (95% CI 0.76-1.09) 0 to 0.5 drinks/day RR=0.84 95% CI 0.70-1.01)

Authors' conclusion	Compared with abstainers and heavier drinkers, persons who consume 0.5 to 1.0 drinks per day have a lower risk of hip fracture. Although available evidence suggests a favorable effect of alcohol consumption on bone density, a precise range of beneficial alcohol consumption cannot be determined.
Reviewer's notes	

Table 19: AMSTAR assessment for Berg 2008

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Not stated for review or included study authors

Briasoulis 2012

Table 20: Data extraction form for Briasoulis 2012

General information	Systematic Review	Yes
	Title	Alcohol Consumption and the Risk of Hypertension in Men and Women: A Systematic Review and Meta-Analysis
	Country of origin	SR: USA
	Source of funding	NR
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	The objective of the present study was to perform a systematic review and meta-analysis of the published prospective studies to separately assess the risk of development of hypertension over a long-term period among men and women based on their levels of alcohol consumption.
	Search Methods	MEDLINE, PubMed, Embase, and the Cochrane Library for Central Register of Clinical Trials using the MESH terms ''alcohol,'' ''hypertension,'' ''blood pressure,'' and the names of individual alcoholic beverages. Human subjects and English language in peer-reviewed journals from 1990 to May 2012. Additionally, a manual search of all relevant references from the screened articles and reviews was performed for additional clinical studies
	Level of evidence (lowest identified)	Level II
	Study types identified	Prospective cohort
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	NR
	Inclusion criteria	(1) prospective studies assessing the effects of alcohol consumption on long-term risk of hypertension;

		(2) studies reporting outcomes of interest, including number of patients who developed hypertension; and (3) at least 3 different non-overlapping levels of drinking categories to allow estimation of dose-response relationship; and (4) studies with at least 1 year of follow-up in each study arm.
	Exclusion criteria	(1) persons who consumed alcohol used as controls; (2) absence of quantitative description of endpoints; (3) lack of clear and reproducible results; and (4) studies in the abstract form without a published manuscript in a peer-reviewed journal.
Exposure	Definition	Alcohol consumption categories
	Method of measurement	Measurement of alcohol consumption varied among studies. Therefore alcohol consumption data were converted into the same unit (g/d).
	Reference category	Non-drinker In the majority of studies, lifetime abstainers and former drinkers were combined into one category, ''nondrinkers,'' thus leading to limited information about risk of hypertension for these two groups separately.
	Statistical approach	men were categorized into 7 drinking categories based on increments of 10 g/d of alcohol consumption: abstainers (nondrinkers), <10 g/d, 10 to 20 g/d, 20 to 30 g/d, 30 to 40 g/d, 40 to 50 g/d, and >50 g/d. Similarly, women were categorized into 5 groups: abstainers (nondrinkers), <10 g/d, 10 to 20 g/d, 20 to 30 g/d, and 30 to 40 g/d. Assigned the level of alcohol consumption from each study to these groups based on the midpoint of the upper and lower boundaries in each category as the average intake. This categorization of alcohol drinking makes possible the comparison of heterogeneous classification of alcohol intake among the different studies and at the same time allows inclusion of data from studies in which precise information on levels of alcohol consumption were not available. When the upper bound of the highest category was not specified, we used the range of the previous reported category. The alcohol habits were assumed to be stable during the follow-up period.
Results: (per outcome)	Definition of outcome	long-term risk of developing hypertension.
	Method of measurement	NR
	No. of studies and participants analysed by type of study	16 prospective studies included in the analysis 33,904 men and 193,752 women
	No. of studies and participants excluded or missing (with reasons) by type of study	Excluded: 2 studies, poor study design, insufficient data Excluded after reading title/abstract as did not satisfy inclusion criteria (n=32) One study by Klatsky colleagues was excluded because it did not separately report the effects of alcohol consumption on men and women
	Statistical method of analysis	Heterogeneity was assessed with the I2 statistic, with I2 <25% considered low and I2 >75% considered high. Small study effect, including publication bias, was tested using funnel plot and Egger test. DerSimonian–Laird random-effects model for relative risk (RR)
	Significance/direction	Light to moderate alcohol consumption may have the similar risk as non-drinking. Heavy drinking is associated
	Heterogeneity	None for highest category for both genders, moderate for <10g men, 41-50g men, significant for the remaining categories.
	Results	Publication Bias: The funnel plots did not show marked asymmetry and all Egger's tests were not significant. The average follow-up duration was 7.6 years for women and 9.8 years for men. In men, the random-effects model showed a significantly increased risk of hypertension with alcohol consumption of 31 to 40 g/d (RR, 1.77; 95% confidence interval [CI], 1.39–2.26; P<.001) and >50 g/d (RR, 1.61; 95% CI, 1.31–1.87; P<.001). There was a trend towards increased risk of hypertension with alcohol consumption of <10 g/d (RR, 1.03; 95% CI, 0.94–1.13; P=.51), 11 to 20 g/d (RR, 1.15; 95% CI, 0.99–1.33; P=.06), 21 to

		30 g/d (RR, 1.07; 95% CI, 0.86–1.34; P=.54), and 41 to 50 g/d (RR, 1.17; 95% CI, 0.84–1.65; P=.34) In women, the random-effects model showed a significantly decreased risk of hypertension with alcohol consumption of <10 g/d (RR, 0.87; 95% CI, 0.82–0.92; P<.001) and a trend toward decreased risk of hypertension with alcohol consumption 11 to 20 g/d (RR, 0.9; 95% CI, 0.87–1.04; P=.17). The meta-analysis revealed a significantly increased risk of hypertension with alcohol consumption of 31 to 40 g/d (RR, 1.19; 95% CI, 1.07–1.32; P=.002) and a trend toward increased risk of hypertension with alcohol consumption of 21 to 30 g/d (RR, 1.16; 95% CI, 0.91–1.46; P=.23).
Authors' conclusion	Alcohol consumption in moderation is associated with a reduced risk of HF. The pooled adjusted RRs of HF were 0.85 [95% CI 0.78–0.93] for light to moderate alcohol consumption (<14 drinks/week) and 0.90 (95% CI 0.72–1.13) for high alcohol consumption (≥14 drinks/week) compared with non-drinkers.	
Reviewer's notes		

Table 21: AMSTAR assessment for Briasoulis 2012

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	No	Confounders not stated
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in	No	
9	Were the methods used to combine the findings of studies	No	Heterogeneity not explored
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Not stated for review or included study authors

Knott 2015

Table 22: Data extraction form for Knott 2015

General information	Systematic Review	Yes
	Title	Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies
	Country of origin	SR: UK
	Source of funding	C.K., S.B., and A.B. are funded by the European Research Council (ERC-StG-2012-309337_AlcoholLifecourse; principal investigator A.B. [http://www.ucl.ac.uk/alcohol-lifecourse]) and the U.K. Medical Research Council/Alcohol Research UK (MR/M006638/1).
	Possible conflicts of interest (for study authors or translators)	No potential conflicts of interest relevant to this article were reported.
AMSTAR Rating		7
Characteristics of review and included primary studies	Aim/objectives of systematic review	Observational studies indicate that moderate levels of alcohol consumption may reduce the risk of type 2 diabetes. In addition to providing an updated summary of the existing literature, this meta-analysis explored whether reductions in risk may be the product of misclassification bias.

	Search Methods	PubMed (MEDLINE), Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Alcohol and Alcohol Problems Science (ETOH) databases were searched for relevant studies. Where possible, searches identified publications with titles or abstracts containing an alcohol-related term ("alcohol," "ethanol," or "drink*"), plus a diabetes related term ("diabet*", "NIDDM," or "T2D*"), plus a term indicative of longitudinal observational data ("cohort,""inciden*", "prospective," "longitudinal," "case," or "retrospective"). No limits were placed upon the language or date of publication, and searches were undertaken on 18 February 2014. Unpublished literature, including conference abstracts and working papers, was not included.
	Level of evidence (lowest identified)	Level IV (case-control)
	Study types identified	Cohort, case-cohort, and nested case-control designs
	Quality of evidence evaluated and summary of RoB	Nos 3-9, median 6
	RoB tool used	NOS
	Inclusion criteria	NR
	Exclusion criteria	NR
Exposure	Definition	NR
	Method of measurement	Method of case ascertainment was summarized as participant self-report (n = 11), objective ascertainment (n = 21), or a combination thereof (n = 6)
	Reference category	33 used a conventional non-current drinking category and 5 included a never-drinking category,
	Statistical approach	Exposure reported in number of drinks was converted to grams per day assuming country-specific standard drinks. Exposures categorized according to periods longer than a day were converted into daily estimates assuming an even distribution of consumption over the reference period. Where averages were not reported for each exposure category, the medians of the lower and upper limits were selected. For categories with no upper limit, median values were defined as 1.5 times the lower limit of the category.
Results: (per outcome)	Definition of outcome	Incident type 2 diabetes
	Method of measurement	The gold standard of the publication period.
	No. of studies and participants analysed by type of study	37 cohort, 1 nested case-control
	No. of studies and participants excluded or missing (with reasons) by type of study	347 duplicates 2255 not on diabetes and alcohol 1 unobtainable 45 reported <3 levels of alcohol exposure 7 insufficient data to estimate g/day across 3 or more levels 7 no sex specific data 1 published data insufficient to calculate RR 1 contaminated reference group 8 duplicates
	Statistical method of analysis	ORs and HRs were considered equivalent to RRs for the purpose of the meta-analysis.
	Significance/direction	moderate alcohol drinking may have a protective effect
	Heterogeneity	I2 of 75% (95% CI 67–80) along the first-order polynomial and 50% (95% CI 31–63) along the second-order polynomial. Asian (n = 13) or non-Asian (n = 25) population. No reduction in risk was found within data drawn from Asian populations, with reductions in risk specific to participants from non-Asian regions

	Results	15 studies reported crude or age-adjusted estimates (n = 14), with 23 studies providing multivariable-adjusted data (n = 24). Relative to all abstainers (current nondrinkers and never drinkers), a reduction in the risk of type 2 diabetes appeared present at all levels of alcohol intake ,63 g/day, with risks increasing above this threshold. Peak risk reduction was present between 10–14 g/day, with an 18% decrease in risk relative to combined abstainers. The nonlinear model offered a better parameterization of the dose-response relationship than a linear regression (P #0.001).
Authors' conclusion	Reductions in risk among moderate alcohol drinkers may be confined to women and non-Asian populations. Although based on a minority of studies, there is also the possibility that reductions in risk may have been overestimated by studies using a referent group contaminated by less healthy former drinkers.	
Reviewer's notes		

Table 23: AMSTAR assessment for Knott 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion	No	
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies not provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Lonnroth 2008

Table 24: Data extraction form for Lonnroth 2008

General information	Systematic Review	Yes
	Title	Alcohol use as a risk factor for tuberculosis – a systematic review
	Country of origin	SR: Switzerland
	Source of funding	WHO. Declared no external funding.
	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		5
Characteristics of review and included primary studies	Aim/objectives of systematic review	To determine if there is a likely causal association between alcohol use and risk of TB disease.
	Search Methods	Searched 16,527 articles in a comprehensive private collection of scientific tuberculosis publications (compiled by Dr Hans Rieder) of which a copy is kept at the Stop TB Department at the World Health Organization. Keywords "alcohol" or "alcoholism". PubMed. Keywords "alcohol OR alcoholism AND tuberculosis". Dates not stated. Reference lists of all reviewed articles were screened.

	Level of evidence (lowest identified)	Level IV.
	Study types identified	Cohort Case-control
	Quality of evidence evaluated and summary of RoB	No RoB assessment Bias caused by different approaches for the selection of controls in the case control studies may also have contributed to the heterogeneity. Several of the case control studies used hospital controls or controls recruited among other groups, such as prisoners and social service clients, that are likely to have higher alcohol intake levels than the general population. There might have been residual confounding that could have biased the pooled estimate across the studies.
	RoB tool used	None
	Inclusion criteria	Case-control and cohort studies Individual level data on alcohol exposure (amount of alcohol intake or a clinical diagnosis of an alcohol use disorder) and active TB disease Reports the crude or adjusted odds ratio, or crude data from which odds ratios could be calculated
	Exclusion criteria	Not stated. Subsequently excluded small studies after publication bias suspected.
Results: (per outcome)	Definition of outcome	Active TB disease
	Method of measurement	Mainly self-reported alcohol consumption.
	No. of studies and participants analysed by type of study	18 Case-control, (Cases=4305, controls=4684) 3 Cohort (n=60,624)
	No. of studies and participants excluded or missing (with reasons) by type of study	Not stated.
	Statistical method of analysis	Random and fixed effects meta-analysis.
	Significance/direction	High exposure to alcohol >40g per day, is associated with increased odds of tuberculosis.
	Heterogeneity	Cochrane's Q p-value and I2. I2
	Results	The low-exposure category (4 studies) included those studies that defined exposure as alcohol use above a cut-off point that was set at a level below 40 g (or 50 ml) alcohol per day. The high-exposure category (5 studies) included studies that defined exposure as alcohol consumption above a cut-off set at a level above 40 g per day. The third category included 6 studies that had ascertained a diagnosis of alcohol use disorder from medical records. High exposure category (11 studies) OR = 3.50 (95% CI: 2.01–5.93) Low exposure category (4 studies) OR = 1.08, 95% CI: 0.82–1.40 Sensitivity analysis: After exclusion of the three studies that had the highest standard error, because of suspected publication bias, the pooled effect sizes for studies in the high-exposure category was 2.94 (95% CI 1.89–4.59). Confounding variables sensitivity analysis in high-exposure group: Controlled* for HIV status 3.26 (2.26–4.70) Controlled* age, sex, SES, 3.49 (2.06–5.90) Controlled* HIV, age, sex, SES, smoking 4.08 (2.49–6.68) Controlled* infection, age, sex, SES 4.21 (2.73–6.48) Excluding three smallest studies and Brown I and Kim (highest and lowest effect sizes) 2.96 (2.28–3.85) Pulmonary TB cases only 3.67 (2.58–5.22) All types of TB 2.87 (1.47–5.58)

Authors' conclusion	There is a three-fold risk increase of active TB associated with consumption of more than 40 g alcohol per day, and/or having an alcohol use disorder.
Reviewer's notes	Funnel plots for publication bias: suspected. Population: Some included studies only on smokers but smoking adjusted for in analysis. Other studies do not adjust for smoking as a confounder.

Table 25: AMSTAR assessment for Lonnroth 2008

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	Suspected
11	Was the conflict of interest stated? [k]	Yes	Declared no conflicts of interest

Larsson 2014

Table 26: Data extraction form for Larsson 2014

General information	Systematic Review	Yes
	Title	Alcohol Consumption and Risk of Atrial Fibrillation: A Prospective Study and Dose-Response Meta-Analysis
	Country of origin	SR: Sweden
	Source of funding	Research grant from the Swedish Research Council
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		4
Characteristics of review and included primary studies	Aim/objectives of systematic review	To examine the dose-response association of alcohol consumption with risk of AF and to assess whether light to moderate alcohol consumption increases the risk.
	Search Methods	Searched PubMed to January 10, 2014 using search terms alcohol consumption, alcohol drinking, or alcohol intake combined with atrial fibrillation or flutter. Reference lists of reviews and included studies were checked.
	Level of evidence (lowest identified)	II
	Study types identified	Prospective cohort studies
	Quality of evidence evaluated and summary of RoB	N/A but limited to prospective cohort studies.
	RoB tool used	None.
	Inclusion criteria	1) prospective design; 2) the exposure was alcohol consumption; 3) the outcome was incidence of AF or AF and AFL combined; and 4) RRs with 95% CIs were reported for at least 3 categories of alcohol consumption to be able to estimate a dose-response trend.
	Exclusion criteria	AF recurrence.
Exposure	Definition	Alcohol as grams per day
	Method of measurement	Converted alcohol consumption into drinks/day assuming that 1 drink contains 12 g of alcohol.
	Reference category	Varied by study, included none, <1 drink per week, <1.1g/day and <4.1g/day.
	Statistical approach	Dose-response meta-analysis
Results: (per outcome)	Definition of outcome	Incidence of AF or AF and AFL combined
	Method of measurement	NR
	No. of studies and participants analysed by type of study	7 prospective cohort studies n=198,485, cases=11,419
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random-effects and fixed-effects meta-analysis Statistical heterogeneity among studies was evaluated by using the p and I2 statistics. Publication bias was examined with Egger's test. When results were presented separately for men and women (2 studies) results were combined the RR estimates, using a random effects model and included the pooled estimate in the meta-analysis. In a sensitivity analysis, results combined for the RR estimates by using a fixed effects model. To evaluate a potential nonlinear association of alcohol consumption with AF risk, a restricted cubic spline model with 3 knots at percentiles 25%, 50%, and 75% of the distribution was used. A p value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.
	Significance/direction	Significant dose-response relationship
	Heterogeneity	0% none detected

	Results	No publication bias detected. The linear dose-response analysis reported that for every 12g per day of ethanol consumption the RR increased by 1.08 (95% CI: 1.06 to 1.10).
Authors' conclusion	Alcohol consumption is positively associated with risk of AF. Even moderate consumption of alcohol, which lowers the risk of other cardiovascular diseases, seems to slightly increase the risk of AF.	
Reviewer's notes		

Table 27: AMSTAR assessment for Larsson 2014

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	No	Only search PubMed
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies not provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Larsson 2015

Table 28: Data extraction for Larsson 2015

General information	Systematic Review	Yes
	Title	Alcohol consumption and risk of heart failure: a dose–response meta-analysis of prospective studies
	Country of origin	SR: Sweden
	Source of funding	Supported by a research grant from the Strategic Research Area in Epidemiology (SfoEpi) at Karolinska Institutet.
	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	To assessing the relationship between alcohol consumption and HF risk.
	Search Methods	inception to September 2014. PubMed search terms 'alcohol consumption', 'alcohol drinking', or 'alcohol intake' combined with 'heart failure' and 'prospective study' or 'cohort study'. The reference lists of pertinent articles were reviewed to identify additional studies.
	Level of evidence (lowest identified)	Level II
	Study types identified	Prospective cohort
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	NR
	Inclusion criteria	the study was prospective;

		the exposure was alcohol consumption; the outcome was HF incidence (hospitalization) and/or mortality; the population was free from HF at baseline relative risks (RRs) with 95% confidence intervals (CIs), adjusted for at least age, were reported.
	Exclusion criteria	NR
Exposure	Definition	Light to moderate alcohol consumption as a median intake of <14 drinks/week and high consumption as a median intake of ≥14 drinks/week.
	Method of measurement	12g alcohol considered standard drink
	Reference category	Non-drinkers (not restricted to lifetime abstainers)
	Statistical approach	For each study, they assigned the median or mean alcohol consumption for the category to each corresponding RR. When the median or mean consumption was not reported, they assigned the midpoint of the upper and lower boundaries in each category as the median consumption. If the upper boundary for the highest category was not provided, they assumed that the boundary had the same amplitude as the adjacent category. When the lowest category was open-ended, we set the lower boundary to zero.
Results: (per outcome)	Definition of outcome	Heart failure
	Method of measurement	HF incidence (hospitalization) and/or mortality
	No. of studies and participants analysed by type of study	8 prospective cohorts, n=202,378, cases=6211
	No. of studies and participants excluded or missing (with reasons) by type of study	Excluded based on title and/or abstract (n = 124) No relative risks were provided for the association between alcohol consumption and HF (n = 3) Included prevalent cases of HF (n = 1) Same source population as one of the included studies and included hypertensive men only (n = 1)
	Statistical method of analysis	two-stage random-effects dose–response meta-analysis: a restricted cubic spline model using generalized least square regression restricted maximum likelihood method in a random-effects meta-analysis
	Significance/direction	Moderate alcohol consumption may be associated with a reduced risk of heart failure, however higher levels of alcohol consumption may not infer a different risk when compared to non-drinkers.
	Heterogeneity	Moderate heterogeneity. I2 = 39.2% for light to moderate consumption. I2 = 41.3% for high consumption.
	Results	Compared with non-drinkers, the RRs (95% CI) of HF across levels of alcohol consumption were 0.90 (0.84–0.96) for 3 drinks/week, 0.83 (0.73–0.95) for 7 drinks/week, 0.90 (0.73–1.10) for 14 drinks/week, and 1.07 (0.77–1.48) for 21 drinks/week. The pooled RRs of HF for light to moderate and high alcohol consumption were 0.85 (95% CI 0.78–0.93; I2 =39.2%) and 0.90 (95% CI 0.72–1.13; I2 =41.3%), Separated light from moderate alcohol consumption (does not define what light or moderate is), the pooled RRs were 0.87 (95% CI 0.82–0.93; I2 =0%) for light consumption (eight studies) and 0.80 (95% CI 0.65–0.97; I2 =65%) for moderate consumption (five studies) In a sensitivity analysis in which one study at a time was excluded and the rest analysed, the RR for light to moderate drinkers vs. non-drinkers ranged from 0.82 (95% CI 0.77–0.89) when the study by Wang et al.9 was removed to 0.87 (95% CI 0.80–0.94) when the study by Walsh et al. was excluded. Stratified analysis by study area, the pooled RRs of HF for light to moderate alcohol consumption vs. no consumption were 0.83 (95% CI 0.77–0.89) for the six studies conducted in North America and 0.91 (95% CI 0.72–1.16) for the two European studies.
Authors' conclusion	Alcohol consumption in moderation is associated with a reduced risk of HF.	
Reviewer's notes		

Table 29: AMSTAR assessment for Larsson 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in	No	
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Larsson 2016

Table 30: Data extraction for Larsson 2016

General information	Systematic Review	Yes
	Title	Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis
	Country of origin	SR: Sweden
	Source of funding	Funded by the Swedish Stroke Association. AWo has received funding from the Swedish Research Council/Committee for Research Infrastructures for maintenance of the Swedish cohorts. SCL is supported by a Junior Researcher Award from the Strategic Research Area in Epidemiology at Karolinska Institutet. HSM is supported by a National Institute for Health Research (NIHR) Senior Investigator award, and his work is supported by the Cambridge Universities NIHR Comprehensive Biomedical Research Centre. The funders had no role in the design, collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.
	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		5
Characteristics of review and included primary studies	Aim/objectives of systematic review	The aim of this study was to conduct a meta-analysis of prospective studies assessing the relationship between alcohol consumption and risk of heart failure (HF).
	Search Methods	PubMed January 1966 to September 1, 2016 Search terms “alcohol consumption”, “alcohol drinking”, or “alcohol intake” combined with “stroke”, or “cerebrovascular disease”, or “cerebral infarction”, or “intracerebral hemorrhage” or “subarachnoid hemorrhage”. Searches of the reference lists of identified articles
	Level of evidence (lowest identified)	Level II
	Study types identified	Prospective cohort
	Quality of evidence evaluated and summary of RoB	4-9 NOS
	RoB tool used	Newcastle–Ottawa Scale

	Inclusion criteria	Prospective studies that reported relative risks (RR) with 95 % confidence intervals (CI) for quantitative categories of alcohol consumption in relation to nonfatal or fatal ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage.
	Exclusion criteria	Studies that only reported data on total stroke (ischemic and hemorrhagic strokes combined) or total hemorrhagic stroke
Exposure	Definition	Alcohol consumption
	Method of measurement	Light (<1 drink/day), moderate (1–2 drinks/day), high (>2–4 drinks/day), and heavy (>4 drinks/day) alcohol consumption.
	Reference category	In a sensitivity analysis, we stratified the studies by reference group used.
	Statistical approach	Alcohol consumption was standardized to drinks of alcohol. If alcohol consumption was reported in grams, the values were converted into drinks by assuming that one drink on average contains 12 grams of alcohol. The median or mean alcohol intake for each category was assigned to the corresponding risk estimate. If average values were not reported, each category was assigned the midpoint of the upper and lower boundaries for that category. If an upper boundary was not provided for the highest category, the boundary was presumed to have the same range as the adjacent category.
Results: (per outcome)	Definition of outcome	ischemic stroke intracerebral hemorrhage subarachnoid hemorrhage
	Method of measurement	Nonfatal or fatal
	No. of studies and participants analysed by type of study	3824 ischemic stroke cases (2216 in men and 1608 in women), 555 intracerebral haemorrhage cases (350 in men and 205 in women), and 176 subarachnoid haemorrhage cases (82 in men and 94 in women)
	No. of studies and participants excluded or missing (with reasons) by type of study	2416 not relevant at title/abstract screen 60 full-text articles excluded (30 total stroke only, 15 duplicates, 11 no quantitative categories of alcohol consumption, 3 total cardiovascular disease, 1 alcoholic beverages only)
	Statistical method of analysis	Random-effects model Heterogeneity was evaluated with the I2 statistic Egger's test was used to assess small-study bias such as publication bias Stata used
	Significance/direction	There may be a decreased risk at <2 drinks per day for ischaemic stroke but an increased risk for >2 drink per day, when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers). There may be no difference in risk of intracerebral hemorrhage and subarachnoid hemorrhage at <4 drinks/day but an increased risk at >4 drinks/day when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).
	Heterogeneity	Results did not change in a sensitivity analysis in which the mid-point for the highest category was set at 1.5 times the half range of the preceding category.
	Results	Categorical random effects meta-analysis for risk of ischemic stroke reported RR=0.90 (95% CI, 0.85–0.95, 20 studies, I2=23.7%), <1 drink/day, RR=0.92 (95% CI, 0.87–0.97, 20 studies, I2=0%) for 1–2 drinks/day, RR=1.08 (95% CI, 1.01–1.15, 21 studies, I2=0%) >2–4 drinks/day, and RR=1.14 (95% CI, 1.02–1.28, 12 studies, I2=9.9%) for more than 4 drinks/day, when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers). For <3 drinks/week RR=0.89 (95% CI, 0.84–0.94; I2 = 20%) and for 3-7 drinks/week RR=0.90 (95% CI, 0.83–0.98; I2 = 23.6%). Categorical random effects meta-analysis for risk of ischemic stroke reported <1 drink/day (RR=0.92 (95% CI, 0.77–1.10, 9 studies, I2=30.3%), for 1-2 drinks/day RR=0.99 (95% CI, 0.82–1.18, 8 studies, I2=0%), for >2-4 drinks/day RR=1.25 (95% CI, 1.01–1.15, 8 studies, I2=0%) >2–4 drinks/day, and RR=1.25 (95% CI, 0.93–1.67, 8 studies, I2=9.9%) for more than 4 drinks/day (RR = 1.67; 95 % CI, 1.25–2.23, 8 studies, I2=57.3%), when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers). Categorical random effects meta-analysis for risk of subarachnoid

		hemorrhage reported <1 drink/day (RR=1.21 (95% CI, 0.96–1.52, 9 studies, I2=18.9%), for 1-2 drinks/day RR=1.11 (95% CI, 0.80–1.53, 6 studies, I2=0%), for >2-4 drinks/day RR=1.39 (95% CI, 0.94–2.07, 8 studies, I2=0%) and for more than 4 drinks/day RR = 1.82 (95 % CI, 1.18–2.82, 8 studies, I2=39.1%%), when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).
Authors' conclusion	Findings from this meta-analysis indicate that alcohol consumption has divergent effects on different stroke types. This may explain some of the inconsistent results from previous studies associating alcohol consummation with all strokes.	
Reviewer's notes		

Table 31: AMSTAR assessment for Larsson 2016

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	Not mentioned for data extraction but 2 reviewers undertook study selection.
3	Was a comprehensive literature search performed? [c]	No	Only one database searched
4	Was the status of publication (i.e. grey literature) used as an inclusion	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in	Yes	Stratified analysis conducted for NOS <7 or ≥7
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Mostofsky 2016

Table 32 Data extraction form for Mostofsky 2016

General information	Systematic Review	Yes
	Title	Alcohol and Immediate Risk of Cardiovascular Events
	Country of origin	11 studies in Europe, 1 in Russia, 4 in US, 2 in New Zealand, 4 in Australia, 1 in 52 countries worldwide.
	Source of funding	Dr Mostofsky received support from the a National Institutes of Health (grant L30-HL115623-02) and a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100). The content is solely the responsibility of the authors and does not necessarily represent the official views of the European Research Council, Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or The National Institutes of Health. Mr. Chahal received support from the Frederick Banting and Charles Best Canada Graduate Scholarship and the Michael Smith Foreign Study Supplement from the Canadian Institutes of Health Research. No funding organization had any role in the design and conduct of the study; collection; management, analysis and interpretation of the data; and preparation of the manuscript.

	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		6
Characteristics of review and included primary studies	Aim/objectives of systematic review	To determine the association between alcohol consumption and cardiovascular events experienced in the following days or hours after alcohol intake.
	Search Methods	One person (Dr Mostofsky) performed a literature search of the CINAHL, Embase, and PubMed databases from January 1966 through March 2015 by using free-text words and Medical Subject Headings terms without language restrictions. We also reviewed the reference lists of retrieved articles.
	Level of evidence (lowest identified)	Case-crossover not in NHMRC hierarchy but assume Level IV.
	Study types identified	Case-control Case-crossover
	Quality of evidence evaluated and summary of RoB	The SR considered the following factors important for quality recording the timing between the onset of the cardiovascular event and ascertainment of alcohol intake, whether alcohol intake was assessed with an interview or questionnaire whether proxy respondents provided information on alcohol intake.
	RoB tool used	None
	Inclusion criteria	(1) the design was a cohort, case-control, self-controlled case series or case-crossover study; (2) the investigators reported relative risks (RRs) and 95% confidence intervals (CIs) for the association between alcohol intake and MI, IS, or HS; (3) the investigators retrospectively evaluated alcohol intake directly from the participant or by proxy for the 1-week period before event onset.
	Exclusion criteria	Studies that evaluated the impact of laboratory-administered alcohol on myocardial ischemia, arrhythmia, atrial fibrillation, or intermediate outcomes such as blood pressure or cardiovascular reactivity.
Exposure	Definition	Alcohol consumption
	Method of measurement	Retrospectively evaluated alcohol intake directly from the participant or by proxy for the 1-week period before event onset.
	Reference category	No alcohol consumption
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	Ischemic stroke Myocardial infarction Haemorrhagic stroke
	Method of measurement	The change in cardiovascular risk immediately following any alcohol intake in comparison with no alcohol intake.
	No. of studies and participants analysed by type of study	23 studies (16 case-control, 7 case-crossover) 29457 participants Ischemic stroke: One case-crossover and 8 case-control studies Myocardial Infarction: 5 case-crossover and 4 case-control studies Haemorrhagic Stroke: One case-crossover and 6 case-control studies
	No. of studies and participants excluded or missing (with reasons) by type of study	Myocardial Infarction: One study reported a higher risk of sudden cardiac death within 2 hours after alcohol consumption (RR, 3.00; 95% CI, 1.61–5.68), but was not included in the analyses because the cause of death may have been attributable to cardiomyopathy or arrhythmias.
	Statistical method of analysis	Random-effects model for meta-analysis 2-stage random-effects dose–response meta-analyses.
	Significance/direction	U-shaped association between alcohol intake and MI risk, IS risk
	Heterogeneity	Considerable heterogeneity for MI within 24 hours (I2=75.7%) Moderate heterogeneity for IS within 24 hours (I2=48.6%) IS within one week I2=36.8%

		Sensitivity analyses included estimates from case-control studies that did not account for confounders. Considerable heterogeneity for HS within 24 hours (I2=89.8%). HS within one week I2=32.5% Sensitivity analysis was conducted by removing one study at a time and results were similar.
	Results	Myocardial Infarction: The greatest benefit following ≈28 g of alcohol (≈2 drinks) in 1 day (RR, 0.67) and a higher risk following ≈108 g (≈9 drinks) in 1 day (RR, 1.59). Within a week following alcohol consumption, there was a lower risk of MI with moderate alcohol intake but a higher risk following heavy alcohol consumption. Two studies assessed MI risk within 1 week among men, with one21 reporting a lower MI risk (RR, 0.25; 95% CI, 0.13–0.50) after ≈18 g of alcohol in the past week and the other reporting higher risk of death from ischemic heart disease or MI after heavy alcohol intoxication for ≥2 days when the person is withdrawn from normal social life (RR, 3.57; 95% CI, 1.65–7.73). U-shaped association between alcohol intake and MI or coronary event (Pcurve<0.001). 4 Case-control (cases n=1398, controls n=3282), 5 Case-crossover, n=18,297 Ischemic Stroke: U-shaped association between alcohol intake and IS (Pcurve=0.007) (1 case-crossover, 7 case-control). It reported a lower risk of IS for ≈75g alcohol consumption and a 2.25-fold higher risk of IS in the week following ≈225g, within 1 week after drinking alcohol compared to not drinking alcohol (I2=8.6%). A dose-response relationship was reported for IS within 24 hours (Pcurve=0.03, Plinearity=0.52). RR=0.94 (95% CI 0.66—1.32) for IS in 24 hours (1 case-crossover, 4 case-control studies) RR=0.84 (95% CI 0.59-1.19) within one week (4 case-control studies) for any alcohol consumption compared to not drinking, with moderate heterogeneity (I2=48.6%, I2=36.8%, respectively). Hemorrhagic Stroke: U-shaped association between alcohol intake and HS (Pcurve=0.02). It reported a 38% lower risk of HS with ≈48g of alcohol but an increased risk of 1.26-fold of HS with ≈81g within 24 hours of consumption in comparison with no intake (I2=90.5%). A dose-response relationship was reported for HS within one week (Pcurve<0.001, Plinearity=0.42, I2=8.3%). RR=0.81 (95% CI 0.23-2.81) of HS in 24 hours for any alcohol consumption compared to no drinking, but with significant heterogeneity (I2=89.8%). The risk of HS increased when the outcome was measured up to 1 week after alcohol consumption, RR=3.33 (95% CI 1.82-6.09) for any alcohol consumption compared to no drinking risk in the following day.
Authors' conclusion	There appears to be a consistent finding of an immediately higher cardiovascular risk following any alcohol consumption, but, by 24 hours, only heavy alcohol intake conferred continued risk.	
Reviewer's notes	No publication bias detected.	

Table 33 AMSTAR assessment for Mostofsky 2016

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? a	No	
2	Was there duplicate study selection and data extraction? b	Yes	
3	Was a comprehensive literature search performed? c	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? d	No	
5	Was a list of studies (included and excluded) provided? e	No	
6	Were the characteristics of the included studies provided? f	Yes	
7	Was the scientific quality of the included studies assessed and documented? g	No	
8	Was the scientific quality of the included studies used	No	

	appropriately in formulating conclusions? h		
9	Were the methods used to combine the findings of studies appropriate? i	Yes	
10	Was the likelihood of publication bias assessed? j	Yes	
11	Was the conflict of interest stated? k	No	Only stated for review authors

O'Keefe 2014

Table 34: Data extraction for O'Keefe 2014

General information	Systematic Review	Yes
	Title	The effect of moderate gestational alcohol consumption during pregnancy on speech and language outcomes in children: a systematic review
	Country of origin	Ireland
	Source of funding	HRB in Ireland under Grant no. PhD/2007/16
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To assess the effect of low to moderate levels of alcohol consumption during pregnancy (up to 70 grams of alcohol per week) compared to abstinence on speech and language outcomes in children
	Search Methods	Searched Embase, PubMed, Cinahl, SCOPUS, Web of Knowledge and The Cochrane Library up to 1 March 2012. MeSH terms were used. Reference lists of retrieved articles were handsearched for additional references. Authors of one included study were contacted for additional information
	Level of evidence (lowest identified)	III-2
	Study types identified	Cohort studies
	Quality of evidence evaluated and summary of RoB	Ranged from 'minimal' to 'high' bias based on selection and confounding. Information was provided on how studies were rated according to selection, exposure, outcome assessment, confounding factor, analytical and attrition bias
	RoB tool used	Bias Classification Tool developed by McDonald et al 2009
	Inclusion criteria	(1) exposure: alcohol consumption (low to moderate alcohol consumption vs not drinking); (2) outcomes: any measure or component of language, speech and communication delay, development or disorder (e.g. acquired language disorders and semantic pragmatic disorders); (3) design: case control or cohort studies; and (4) effect size: any available measures of association including odds and risk ratios
	Exclusion criteria	Other cognitive and developmental outcomes and nonverbal language outcomes were excluded; Studies of populations with special developmental needs such as autistic spectrum disorder
Exposure	Definition	Low to moderate alcohol exposure defined as an average of less than 10 grams per day or 70 grams per week during pregnancy
	Method of measurement	Collected data on alcohol exposure during pregnancy through direct face-to-face interviews (1 study) while postal survey send to participants after pregnancy (2 studies)
	Reference category	Not drinking during pregnancy
	Statistical approach	Not done. Wide variation in exposure and outcomes across the 3 studies meant that meta-analyses were not possible
Results: (per outcome)	Definition of outcome	Communication (language) delay
	Method of measurement	Communication scale from Ages and Stages Questionnaire
	No. of studies and participants analysed by type of study	1 study (1,739 women)
	No. of studies and participants excluded or missing (with reasons) by type of study	Study at moderate risk of attrition bias (11 to 20% attrition but reasons not provided)
	Statistical method of analysis	Not applicable
	Significance/direction	Non-significant for unadjusted and adjusted ORs provided at Trimesters 1, 2 and 3
	Heterogeneity	Not applicable
	Results	Unadjusted OR Trimester 1: 0.95 (95% CI 0.68 to 1.34), Trimester 2: 0.88 (95% CI 0.63 to 1.23) and Trimester 3: 0.83 (0.60 to 1.17) Adjusted OR Trimester 1: 0.97 (95% CI 0.65 to 1.43), Trimester 2: 0.87 (95% CI 0.59 to 1.28), Trimester 3: 0.84 (95% CI 0.57 to 1.23) "Data show unadjusted and confounder adjusted odds ratios for the probability of language delay among

		low drinkers compared to women who are abstinent at the same time point." "All results show reduced odds among low drinkers but results are not statistically significant as indicated by the confidence intervals which span the null value of an odds ratio equal to 1".
Results: (per outcome)	Definition of outcome	Communication development
	Method of measurement	7-item language measure of the Denver Developmental Scale (1 study) or Sequenced Inventory of Communication Development (SICD; 1 study)
	No. of studies and participants analysed by type of study	2 studies in total (13,417 women + 618 women)
	No. of studies and participants excluded or missing (with reasons) by type of study	Studies at moderate (11 to 20% but reasons for loss to follow-up not explained) to high risk (> 20% attrition and reasons for loss to follow-up not explained) of attrition bias
	Statistical method of analysis	Not applicable
	Significance/direction	1 study provided the mean number of drinks per day for scores of 0 to 7 (low to high levels of language development). 1 study provided the mean age-adjusted SICD scores at 1,2 and 3 years for expressive and receptive language (no details about the scale)
	Heterogeneity	Not applicable
	Results	Mean number of drinks per day study (0 to 7 reflect low to high levels of language development): 0/7: 0.47 (0.37; 95% CI) 1/7: 1.64 (1.28) 2/7: 0.23 (0.10) 3/7: 0.57 (0.17) 4/7: 0.58 (0.12) 5/7: 0.57 (0.09) 6/7: 0.74 (0.14) 7/7: 0.65 (0.10) 1 study provided the mean age-adjusted SICD scores at 1,2 and 3 years of age for the outcome expressive language: -1/3 drink per day vs abstinence: 1 year = 25.5 (95% CI 25.0 to 26.5), 2 years = 30.0 (95% CI 28.5 to 31.0) and 3 years = 30.0 (28.0 to 32.0) -greater than 1/3 drinks and up to 1.5 drinks per day vs abstinence: 1 year = 26.0 (95% CI 25.0 to 27), 2 years = 29.0 (95% CI 27.0 to 32.0) AND SICD scores at 1,2 and 3 years of age for the outcome receptive language: -1/3 drink per day vs abstinence: 1 year = 24.0 (95% CI 23 to 25), 2 years = 39.0 (95% CI 37.0 to 40.0); 3 years = 24.0 (95% CI 23.0 to 25.0) -greater than 1/3 drinks and up to 1.5 drinks per day vs abstinence: 1 year = 24.0 (22 to 25); 2 years = 38.0 (36.0 to 40.0); 3 years = 25.0 (23.0 to 27.0) No significant differences in expressive or receptive language development at 1, 2 or 3 years were evident
Authors' conclusion	"Studies included in this review do not provide sufficient evidence to confirm or refute an association between low to moderate alcohol use during pregnancy and speech and language outcomes in children"	
Reviewer's notes		

Table 35: AMSTAR assessment for O'Keefe 2014

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	The review was not registered with PROSPERO
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	A list of excluded studies was not provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Used a Bias Classification Tool that assessed selection, exposure, outcome, confounding, analytical and attrition bias
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	Review authors explained that pooling was not possible due to heterogeneous nature of exposure and outcomes assessed

10	Was the likelihood of publication bias assessed? [j]	No	
11	Was the conflict of interest stated? [k]	Yes	

Patra 2011

Table 36: Data extraction for Patra 2011

General information	Systematic Review	Yes
	Title	Dose–response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)—a systematic review and meta-analyses
	Country of origin	SR: Canada
	Source of funding	This work was financially supported by a small contribution from the Global Burden of Disease (GBD) Study to the last author. Also, we received support from NIAAA (Alcohol- and Drug-Attributable Burden of Disease and Injury in the US; contract # HHSN267200700041C). In addition, support to the Centre for Addiction and Mental Health (CAMH) for salaries of scientists and infrastructure has been provided by the Ontario Ministry of Health and Long Term Care.
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		4
Characteristics of review and included primary studies	Aim/objectives of systematic review	To review systematically and perform meta-analyses on the effect of maternal alcohol exposure on the risk of low birthweight, preterm birth and small for gestational age (SGA).
	Search Methods	MEDLINE, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science 1 January 1980 and 1 August 2009 Keywords and medical subject headings to identify relevant articles in electronic databases: ('alcohol*' or 'ethanol' or 'light drinking' or 'moderate drinking') AND ('birthweight' or 'low birthweight' or 'gestational age' or 'small for gestational age' or 'preterm*' or 'pregnancy outcome' or 'pregnancy complication' or 'prenatal*') AND ('case' or 'cohort' or 'ratio' or 'risk*' or 'prospective*' or 'follow*')
	Level of evidence (lowest identified)	Level IV
	Study types identified	Cohort Case-control
	Quality of evidence evaluated and summary of RoB	NR for individual studies or overall.
	RoB tool used	STROBE
	Inclusion criteria	1 Reported data were from an original study (i.e. no review articles) 2 Cohort or case–control study in which medically confirmed low birthweight (defined as <2500 g), preterm birth (<37 weeks of gestation) and SGA (<10th percentile of gestational age-adjusted birthweights) were the end points 3 Reporting of relative risk or odds ratios or hazard ratios (or data to calculate these risks) of low birthweight, preterm birth and SGA associated with alcohol consumption.
	Exclusion criteria	letters, editorials, conference abstracts, reviews and comments
Exposure	Definition	Alcohol consumption during pregnancy
	Method of measurement	NR
	Reference category	Abstainers
	Statistical approach	When a range of alcohol intake was given, the midpoint of the range was taken. In cases where open-end for the highest category was given (e.g. 40 +

		g/day), three-quarters of the length of the immediate previous category range was added to the lower bound and was used as the measure. Where consumption was reported in drinks and not in grams, the gram pure alcohol equivalent (of one drink) explained in the article was used as a conversion factor if stated, and if not, conversion was based on geographical location: for Canada 13.6 g, USA 12 g, UK 8 g and for both New Zealand and Australia 10 g pure alcohol. For all other countries without any clear specifications 12 g pure alcohol was used as an equivalent of one drink.
Results: (per outcome)	Definition of outcome	low birthweight, preterm birth and small for gestational age (SGA)
	Method of measurement	incidence, hazard ratios, relative risks or odds ratios
	No. of studies and participants analysed by type of study	SGA: 2 cohort, 6 case-control, n=136,949, n cases=8679 LBW: 15 cohort, 4 case-control, n=277,300, n cases=12,888 Preterm: 12 cohort, 2 case-control, n=280,443, n cases= 12,888
	No. of studies and participants excluded or missing (with reasons) by type of study	1253: no measure of association b/ alcohol, low birthweight, preterm birth and SGA 2: neither cohort nor case–control 38: not enough info to quantify, for each alcohol group, consumption in g/day and assoc RR/OR 6: multiple articles on same study 3: report of alcohol use in combination with illicit drug use 7: systematic reviews or meta-analysis studies
	Statistical method of analysis	Random effects models
	Significance/direction	Dose-response relationship between increased levels of alcohol consumption and increased risk of preterm birth, SGA and LBW.
	Heterogeneity	Overall, marked heterogeneity was found for all birth outcomes (low birthweight (Q = 122.5, P = 0.006; I2 = 80%, 95% CI 73–85%, P < 0.001); preterm birth (Q = 98.03, P < 0.072; I2 = 89%, 95% CI 84–92%, P < 0.001); SGA (Q = 131.20, P < 0.001; I2 = 92%, 95% CI 88–95%, P < 0.001).
	Results	SGA - alcohol consumption below <10g/day compared to non-drinking, was not associated with a risk of SGA. However at >10g/day there was a dose response relationship showing that increased levels of alcohol consumption was associated with increased risk of SGA. At 7 drinks (at US conversion of 12g per drink) per day the RR = 2.02 (1.47-2.77). LBW - alcohol consumption below <10g/day compared to non-drinking, was not associated with a risk of low birthweight. However at >10g/day there was a dose response relationship showing that increased levels of alcohol consumption was associated with increased risk of low birthweight, with 120 g/day RR = 7.48 (95% CI 4.46–12.55). Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately. Preterm birth - alcohol consumption below <19g/day compared to non-drinking, was not associated with a risk of preterm birth. At 36 g/day RR = 1.23 (95% CI 1.05–1.44) compared to not drinking. Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately. Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.
Authors' conclusion	Dose–response relationship indicates that heavy alcohol consumption during pregnancy increases the risks of all three outcomes whereas light to moderate alcohol consumption shows no effect. Preventive measures during antenatal consultations should be initiated.	
Reviewer's notes		

Table 37: AMSTAR assessment for Patra 2011

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	

3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies list not provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	STROBE used but results of quality assessment no reported
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Not stated for included studies

Psaltopoulou 2015

Table 38 Data extraction form for Psaltopoulou (2015)

General information	Systematic Review	Yes
	Title	Alcohol intake, alcoholic beverage type and multiple myeloma risk: a meta-analysis of 26 observational studies
	Country of origin	Greece/Switzerland/UK
	Source of funding	NR
	Possible conflicts of interest (for study authors or translators)	Three authors reported that they received grants from World Cancer Research Fund (WCRF) during the conduct of the study
AMSTAR Rating		5
Characteristics of review and included primary studies	Aim/objectives of systematic review	This meta-analysis aimed to examine the association between alcohol consumption and multiple myeloma risk.
	Search Methods	Searched PubMed to 31 December 2013 using free text. Reference lists were checked.
	Level of evidence (lowest identified)	III-3
	Study types identified	Cohort and case-control studies
	Quality of evidence evaluated and summary of RoB	Ranged from four to eight (mean = 6.69). Reasons for deduction were the use of self-report questionnaires, comparability of ages and other risk factors uncertain, inclusion of hospital-based controls and prior history of multiple myeloma in controls was not assessed
	RoB tool used	Newcastle–Ottawa Scale
	Inclusion criteria	Cohort and case-control studies examining the association between multiple myeloma and alcohol consumption in adults. With overlapping studies, only the larger study was included.
	Exclusion criteria	NR
Exposure	Definition	Alcohol as grams per day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range or 1.2 times the lower bound of an upper, open ended category. Assumed 12.5g per standard drink.
	Reference category	Never drinkers
	Statistical approach	Categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	Multiple myeloma
	Method of measurement	NR
	No. of studies and participants analysed by type of study	26 studies (10 cohorts and 16 case-control, 7,088 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	DerSimonian and Laird random effects meta-analysis. A two-term fractional polynomial model was applied to assess higher order dose-response

		associations. Meta-regression analysis aimed to assess whether gender and age modified any association.
	Significance/direction	Non-significant, no association
	Heterogeneity	Light consumption: I^2=66.4% Moderate consumption: I^2=46.9% Heavy consumption: I^2=2.6%
	Results	Light consumption (ever or current): 0.88 (0.76 – 1.02) Moderate consumption (ever or current): 0.87 (0.77 – 0.99) Heavy consumption (ever or current): 0.86 (0.53 – 1.38) Case-control studies in light drinkers showed a significant decrease in risk. Case-control studies in moderate drinkers showed no association. No difference between study designs in heavy drinkers. Women ever drinkers showed a decreased risk but when only cohort studies included then no association. Ever consumption overall showed a decreased risk mainly due to the case-control studies included. Current or former consumption overall showed no association.
Authors' conclusion	Alcohol intake may confer protection in terms of multiple myeloma risk among females, with wine being particularly beneficial.	
Reviewer's notes		

Table 39 AMSTAR quality assessment for Psaltopoulou 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	Study selection NR. Yes for data extraction.
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	List of included studies provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Newcastle-Ottawa quality scale
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	The effect of the quality of the included studies on the summary estimate was assessed
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	Eggers test
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Yes for review authors, No for included studies

Rehm 2010

Table 40 Data extraction form for Rehm 2010

General information	Systematic Review	Yes
	Title	Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis
	Country of origin	SR: Canada USA (n = 9), Italy (n = 4), Denmark (n = 2), China (n = 1), Japan (n = 1)
	Source of funding	NIAAA (contract # HHSN267200700041C 'Alcohol and Drug-Attributable Burden of Disease and Injury in the US' to the first author) and the Global Burden of Disease and Injury 2005 Project provided financial and/or technical support for this study. In addition, support to Centre for Addiction and Mental Health for salary of scientists and infrastructure has been provided by the

		Ontario Ministry of Health and Long Term Care.
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	To quantify the risk of liver cirrhosis associated with increasing alcohol consumption based on an updated systematic review and meta-analysis of observational studies.
	Search Methods	Ovid MEDLINE, EMBASE, Web of Science, CINAHL, PsychINFO, ETOH and Google Scholar January 1980 to January 2008 Any combination of the key words: alcohol, alcohol consumption, alcohol intake, heavy drinking, liver diseases and liver cirrhosis. Manually reviewed the content pages of the major epidemiological journals and the reference lists of relevant and review articles
	Level of evidence (lowest identified)	IV
	Study types identified	14 Cohort 3 Case-control
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	None.
	Inclusion criteria	i) they had a case–control or cohort design, that is, a stronger level of control than with a cross-sectional study; (ii) hazard ratios, RR or odds ratios and their 95% confidence intervals (CIs) (or information allowing us to compute them) were reported; (iii) the end-point was liver cirrhosis morbidity and/or mortality as defined above; (iv) three or more categories of alcohol consumption were reported, one of them being abstention; (v) clinical assessment of morbidity and mortality (the latter via death certificates).
	Exclusion criteria	Studies were excluded if: they were not published as full reports, such as conference abstracts and letters to editors; a cross-sectional design was used; a continuous measure or only two categories of alcohol consumption were included.
Exposure	Definition	3 or more categories of alcohol consumption
	Method of measurement	Alcohol intake using the categories: 0 (reference group), >0–12, >12–24, >24–36, >36–48, >48–60 and >60 g day-1.
	Reference category	Abstention
	Statistical approach	Assigned the level of alcohol consumption from each study to the categories based on the calculated midpoint of alcohol consumption.
Results: (per outcome)	Definition of outcome	Liver cirrhosis
	Method of measurement	Only studies with clinical defined assessment of morbidity and death certificates for mortality were included (i.e. no, self-reports).
	No. of studies and participants analysed by type of study	14 cohort (n=1,475,765) 3 case-control (n=2122)
	No. of studies and participants excluded or missing (with reasons) by type of study	3071 studies excluded at title/abstract screen 58 excluded at abstract screen (reasons not stated) 41 excluded as did not meet inclusion criteria
	Statistical method of analysis	Fractional polynomial models
	Significance/direction	Dose response relationship between alcohol consumption and morbidity and mortality
	Heterogeneity	Heterogeneity was present in the dose-response models for both women [Q = 200.59, P = 0.001, I2 = 72%, 95% CI (63%, 78%)] and men [Q = 305.22, P = 0.001, I2 = 78%, 95% CI (72%, 82%)] No heterogeneity presented for categorical meta-analysis Sensitivity analysis was conducted but details of what this consisted of what

		not provided and was stated that there was a similar
	Results	Mortality - Women compared to female lifetime abstainers >0–12g RR = 1.9 (1.1, 3.1) >12–24g RR = 5.6 (4.5, 6.9) >24–36g RR = 7.7 (6.3, 9.5) >36–48g RR = 10.1 (7.5, 13.5) >48–60g RR = 14.7 (11.0, 19.6) >60g RR = 22.7 (17.2, 30.1) Mortality - Men compared to male lifetime abstainers >0–12g RR = 1.0 (0.6, 1.6) >12–24g RR = 1.6 (1.4, 2.0) >24–36g RR = 2.8 (2.3, 3.4) >36–48g RR = 5.6 (4.5, 7.0) >48–60g RR = 7.0 (5.8, 8.5) >60g RR = 14 (11.7, 16.7) Morbidity - Women compared to female lifetime abstainers >0–12g RR = 0.4 (0.1, 1.2) >12–24g RR = 1.0 (0.5, 1.9) >24–36g RR = 2.4 (1.8, 3.2) >36–48g RR = 1.9 (1.4, 2.6) >48–60g RR = 5.9 (3.7, 9.3) >60g RR = 6.1 (4.6, 8.0) Morbidity - Men compared to male lifetime abstainers >0–12g RR = 0.3 (0.1, 0.9) >12–24g RR = 0.3 (0.2, 0.4) >24–36g RR = 0.7 (0.5, 1.0) >36–48g RR = 2.0 (1.5, 2.7) >48–60g RR = 2.3 (1.7, 3.2) >60g RR = 5.0 (3.9, 6.4) Continuous dose–response relationship between alcohol consumption and risk of liver cirrhosis in both mortality and morbidity studies. However, the effect of alcohol consumption was greater for mortality in comparison with morbidity studies for both sexes. In mortality studies, compared with women who were lifetime abstainers, the RRs of liver cirrhosis were 4.9 (95% CI 4.0, 6.2) and 12.5 (95% CI 8.8, 17.7) for those who consumed 24 and 60 g of alcohol per day, respectively. In morbidity studies, relative to women who were lifetime abstainers, those who consumed 24 and 60 g of alcohol per day had RRs of 3.2 (95% CI 2.6, 3.9) and 6.2 (95% CI 4.4, 8.7). Although less pronounced, a similar pattern of effect was observed among men.
Authors' conclusion	Alcohol consumption had a significantly greater impact on the risk of liver cirrhosis in studies that had mortality compared with those studies that had morbidity as the end-point.	
Reviewer's notes	Noted: no evidence of substantial publication bias. Large cohort/large sample size Strong dose response relationship	

Table 41 AMSTAR quality assessment for Rehm 2010

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	No	Confounders, age and alcohol levels not stated
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	No	Heterogeneity insufficiently reported and explored.
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Rota 2014b

Table 42 Data extraction form for Rota (2014b)

General information	Systematic Review	Yes
	Title	Alcohol drinking and risk of leukemia—A systematic review and meta-analysis of the dose–risk relation
	Country of origin	Italy/Sweden/USA
	Source of funding	Italian Association of Cancer Research and Italian Foundation for Cancer Research
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		3/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To elucidate and quantify the dose–risk relationship between alcohol drinking and leukaemia risk by conducting a systematic review and meta-analysis of published studies
	Search Methods	Searched PubMed to August 31 2013, using free text. Reference lists of included studies were checked.
	Level of evidence (lowest identified)	III-3
	Study types identified	Cohort and case-control studies
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	None used
	Inclusion criteria	Epidemiological studies published as original articles in English
	Exclusion criteria	• multiple reports on the same study populations, • studies where the levels of alcohol consumption were not quantifiable, • studies not reporting the relative risk or odds ratio (OR) and the corresponding 95% confidence interval (CI), or sufficient information to calculate them, • studies only reporting results for specific alcoholic beverages (i.e., beer, wine and liquor/spirit), when total alcohol consumption was not evaluated, • studies reporting only combined results for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
Exposure	Definition	Alcohol as drinks or grams per day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range or 1.2 times the lower bound for open-ended categories. Assumed 12.5g per standard drink, if not otherwise specified in the original report, 1ml

		= 0.80g, and 1oz = 28.35g.
	Reference category	Occasional/non-drinkers
	Statistical approach	Categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	Leukaemia, including acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), leukaemia not otherwise specified (NOS-LK)
	Method of measurement	NR
	No. of studies and participants analysed by type of study	18 studies (8 cohort and 10 case-cohort, 7,142 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis
	Significance/direction	Non-significant, no association
	Heterogeneity	Leukaemia (overall) • any consumption: I^2=44.9% • light consumption: I^2=35.8% • moderate to heavy consumption: I^2=29.3% ALL • any consumption: I^2=60.4% • light consumption: I^2=83.3% • moderate to heavy consumption: I^2=0.0% CLL • any consumption: I^2=0.0% • light consumption: I^2=32.4% • moderate to heavy consumption: I^2=0.0% AML • any consumption: I^2=60.0% • light consumption: I^2=12.4% • moderate to heavy consumption: I^2=25.8% CML • any consumption: I^2=0.0% • light consumption: I^2=0.0% • moderate to heavy consumption: I^2=24.7% NOS-LK • any consumption: I^2=44.2% • light consumption: I^2=58.2% • moderate to heavy consumption: I^2=49.4%
	Results	Leukaemia (overall) • any consumption: 0.94 (0.85–1.03) • light consumption: 0.90 (0.80–1.01) • moderate to heavy consumption: 0.91 (0.81–1.02) ALL • any consumption: 1.47 (95% CI, 0.47–4.62) • light consumption: 1.42 (0.16–12.49) • moderate to heavy consumption: 1.33 (0.67–2.66) CLL • any consumption: 0.94 (95% CI 0.77–1.15) • light consumption: 0.89 (0.62–1.29) • moderate to heavy consumption: 0.99 (0.78–1.24) AML • any consumption: 1.02 (95% CI, 0.86–1.21) • light consumption: 0.97 (0.85–1.11) • moderate to heavy consumption: 0.90 (0.74–1.09) CML • any consumption: 0.93 (95% CI 0.75–1.14) • light consumption: 0.89 (0.69–1.14)

		• moderate to heavy consumption: 0.99 (0.75–1.32) NOS-LK • any consumption: 0.90 (0.79–1.02) • light consumption: 0.88 (0.82–1.07) • moderate to heavy consumption: 0.90 (0.74–1.10) RR was modified by study design (hospital-based case-control studies, N=3, RR=1.49 (1.19-1.86), I^2=0.0%; population-based case-control studies, N=7, RR=0.85 (0.76-0.95), I^2=25%; p-value for heterogeneity between groups <0.01), geographic area (America, N=8, RR=0.84 (0.76–0.93), I^2=19.8%; Asia, N=4, RR=1.32 (1.02–1.70), I^2=34.9%; p-value for heterogeneity between groups <0.01), reference category (non/occasional drinkers, N=4, RR= 0.77 (0.69–0.87), I^2=0.0%; only non-drinkers, N=14, RR= 1.01 (0.91–1.13), I^2=36.8%; %; p-value for heterogeneity between groups <0.01). RR not modified by sex, age or race. The only significant association in the dose-response meta-analysis was for light drinkers in the cohort studies only for NOS-LK (RR=0.90 (0.81–0.99), N=5, I^2=0.0%) and Leukaemia (RR=0.91 (0.83–0.99), N=5, I^2=0.0%). No significant association was found for any other subtype or pooled estimates of acute, chronic, lymphoid or myeloid leukaemia,
Authors' conclusion	We did not find an increased risk of leukaemia among alcohol drinkers. If any, a modest favourable effect emerged for light alcohol drinking, with a model-based risk reduction of approximately 10% in regular drinkers.	
Reviewer's notes		

Table 43 AMSTAR quality assessment for Rota 2014b

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	Unclear: "Two authors independently carried out a systematic literature search…" "For each study, we extracted the following information:"
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Yes for review authors, No for included studies

Rota 2014c

Table 44: Data extraction for Rota 2014c

General information	Systematic Review	Yes
	Title	Alcohol drinking and cutaneous melanoma risk: a systematic review and dose–risk meta-analysis
	Country of origin	Italy
	Source of funding	Italian Association of Cancer Research

	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	To better quantify the relationship between cutaneous melanoma and alcohol consumption using a meta-analytic approach
	Search Methods	Searched PubMed to April 30, 2012 using MESH headings and free text. Reference lists of reviews and included studies were checked.
	Level of evidence (lowest identified)	III-2
	Study types identified	Cohort and case-control
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	None used
	Inclusion criteria	Epidemiological studies in English
	Exclusion criteria	• studies investigating non melanocytic skin cancer only; • studies reporting neither relative risks (RRs) nor odds ratios (ORs) and the corresponding 95% confidence intervals (CIs), or sufficient information to calculate them; • studies conducted on special populations (e.g. alcoholics or cancer survivors); • studies reporting only the result for specific alcoholic beverages (e.g. beer, wine or liquor/spirit)
Exposure	Definition	Alcohol as grams of ethanol per day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range. Assumed 12.5g per standard drink.
	Reference category	non-drinkers where possible, some included occasional drinkers
	Statistical approach	categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	cutaneous melanoma
	Method of measurement	NR
	No. of studies and participants analysed by type of study	16 studies (2 cohorts and 14 case-control, 6,251 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis
	Significance/direction	Mixed. Some significant associations.
	Heterogeneity	Light consumption: I^2=41.8% Moderate to heavy consumption: I^2=51.0% Adjusted for sun exposure: I^2=60.5%
	Results	light consumption (≤ 1 drink per day): RR 1.10 (95% CI 0.96–1.26) moderate-to-heavy consumption (> 1 drink per day): RR 1.18 (95% CI 1.01–1.40) In studies adjusting for sun exposure: RR 1.12, (95% CI 0.86–1.45)
Authors' conclusion	This meta-analysis of published data reveals that alcohol consumption is positively associated with the risk of CM. However, caution in interpreting these results is required, as residual confounding by sun exposure cannot be ruled out.	
Reviewer's notes		

Table 45 AMSTAR quality assessment for Rota 2014c

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	Duplicate study selection but not data extraction
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	

6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Yes for review authors, No for included studies

Samokhvalov 2010a

Table 46: Data extraction form for Samokhvalov 2010a

General information	Systematic Review	Yes
	Title	Alcohol consumption, unprovoked seizures, and epilepsy: A systematic review and meta-analysis
	Country of origin	SR: Canada Included studies: China, Italy, USA, Nigeria
	Source of funding	Financially supported by contract # HHSN 267200700041C from NIAAA ''Alcohol- and Drug-Attributable Burden of Disease and Injury in the US'' and a small contribution of the Global Burden of Disease (GBD) Study to the last author.
	Possible conflicts of interest (for study authors or translators)	Stated that there were none.
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	To analyse and quantify the association and dose–response relationship between alcohol consumption and epilepsy, with the particular focus on examining potential mechanisms.
	Search Methods	Ovid MEDLINE, EMBASE, Web of Science, CINAHL, PsychINFO, ETOH, and Google Scholar. January 1960 to September 2008 All combinations of the key words: alcohol* (truncated), alcohol, alcohol consumption, alcohol intake, drinking, alcoholism, alcohol abuse, alcohol misuse, epilep* (truncated), epilepsy, epileptic, seizures. Reference lists of relevant articles were reviewed manually
	Level of evidence (lowest identified)	Level IV
	Study types identified	Case-control (6 studies)
	Quality of evidence evaluated and summary of RoB	Several studies included in the meta-analysis did not have clearly defined outcomes.
	RoB tool used	None
	Inclusion criteria	1. A case–control or cohort design. 2. The inclusion of hazard ratios (HRs), relative risks (RRs) or odds ratios (ORs), with 95% confidence intervals (CIs) (or information allowing for their calculation). 3. The endpoint being epilepsy morbidity (as defined by physician) or unprovoked seizures. 4. Three or more categories of alcohol consumption reported (for dose–response analysis).
	Exclusion criteria	1. A cross-sectional design or other designs without any control. 2. Data that did not allow for a calculation of risk for relevant exposure variables. 3. Studies on primarily alcohol-induced seizures as well as any seizures provoked by other factors (strokes, inflammation, etc.).
Results: (per outcome)	Definition of outcome	Epilepsy morbidity, defined by International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)), including unprovoked

		seizures.
	Method of measurement	Defined by physician.
	No. of studies and participants analysed by type of study	6 case-control (cases n=934, controls n=1398)
	No. of studies and participants excluded or missing (with reasons) by type of study	1342 studies excluded (no relevant information) 11 studies excluded (baseline contamination) 1 study excluded (duplication of results)
	Statistical method of analysis	Random-effects models meta-analysis Fractional polynomial models.
	Significance/direction	Alcohol consumption has a dose response relationship with increased risk of epilepsy/unprovoked seizures.
	Heterogeneity	I2 = 9%
	Results	6 studies on risk of epilepsy RR = 2.19 (95% CI 1.83–2.63) for drinkers compared with non-drinkers (this outcome has no dose and is therefore not relevant to the overview). 4 studies on risk of epilepsy RR = 1.29 (95% CI =1.03-1.61) for <50 g daily average consumption of pure alcohol compared with non-drinkers. Dose response: Individuals consuming 12, 48, 72, and 96 g of alcohol daily had RRs of 1.17 (95% CI = 1.13–1.21), 1.81 (95% CI = 1.59–2.07), 2.44 (95% CI = 2.00–2.97), and 3.27 (95% CI = 2.52–4.26), respectively, relative to abstainers.
Authors' conclusion	The dose–response relationship between alcohol consumption and epilepsy and unprovoked seizures was quantified and several pathogenic mechanisms were suggested, although none of them has been shown to be the unique causative pathway for epilepsy. Certain limitations underlying this study require further research to clarify the outstanding statistical issues and pathogenesis of epilepsy in heavy drinkers.	
Reviewer's notes	Reported: No evidence of substantial publication bias.	

Table 47: AMSTAR assessment for Samokhvalov 2010

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	Confounders were not stated
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]		
10	Was the likelihood of publication bias assessed? [j]		
11	Was the conflict of interest stated? [k]		

Samokhvalov 2010b

Table 48: Data extraction form for Samokhvalov 2010b

General information	Systematic Review	Yes
	Title	Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis
	Country of origin	SR: Canada & Germany Included studies: Spain, Finland, USA

	Source of funding	NIAAA (contract no. HHSN267200700041C 'Alcohol- and Drug-Attributable Burden of Disease and Injury in the US' to J.R.), the Global Burden of Disease and Injury 2005 Project, and the Centre for Addiction and Mental Health in Toronto, Canada provided financial and/or technical support for this study. In addition, support to CAMH for salary of scientists and infrastructure was provided by the Ontario Ministry of Health and Long Term Care.
	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		6
Characteristics of review and included primary studies	Aim/objectives of systematic review	(a) quantify the dose–response relationship between alcohol consumption and incidence of CAP; (b) quantify the risk of CAP associated with alcohol-use disorders (AUD); and (c) examine possible pathways.
	Search Methods	Ovid Medline, EMBASE, Web of Science, ETOH and AIM. January 1980 to August 2009 Any combination of the key words 'alcohol', 'alcohol consumption', 'alcohol intake ', 'ethanol', 'alcoholism', 'heavy drinking', and 'pneumonia.' Reference lists of the identified studies were reviewed
	Level of evidence (lowest identified)	Level VI
	Study types identified	Case-control Cohort
	Quality of evidence evaluated and summary of RoB	Not assessed
	RoB tool used	Not assessed
	Inclusion criteria	CAP morbidity and/or mortality as the endpoint. Cohort or case-control study. Dose-response analysis inclusion was also: report risk estimates [HR, RR or OR] with 95% confidence intervals (CIs) across at least three categories of alcohol consumption (e.g. abstainers; 0.1–20 g pure ethanol per day; 21–40 g pure ethanol per day and >40 g pure ethanol per day), or must report sufficient data to estimate these.
	Exclusion criteria	Cross-sectional Not published as full reports e.g. conference abstracts and letters to editors If a continuous measure of alcohol consumption was reported
Results: (per outcome)	Definition of outcome	Community-acquired pneumonia
	Method of measurement	Community-acquired pneumonia morbidity or mortality
	No. of studies and participants analysed by type of study	2 Cohort (n=108658) 3 Case-control (N=3442)
	No. of studies and participants excluded or missing (with reasons) by type of study	1511 studies excluded (no relevant information) 12 studies excluded (baseline contamination; data is not extractable) 2 studies excluded due to potential bias (hospital-acquired pneumonia)
	Statistical method of analysis	To derive the dose–response curve, a fitted family of first- and second-degree fractional polynomial models was used. Random-effects models were used. Statistical heterogeneity among studies was examined using both the Cochrane Q test and the I2 statistic Publication bias: funnel plot, egger's regression asymmetry test and the Begg-adjusted rank correlation test. Stata 10 was used.
	Significance/direction	Risk of pneumonia increased linearly with increasing alcohol consumption. AUD is associated with an increased risk of CAP
	Heterogeneity	3 studies I2 = 0·0% Not shown for AUD
	Results	Association of AUD and the risk of CAP (2 studies) RR 8.22, 95% CI 4.85–13.95) for AUD compared to people without AUD. Onset of CAP and alcohol consumption RR of 1.06 (95% CI 1.01–1.11) per

		standard drink of 12 g pure alcohol per day. Sensitivity analysis removing largest study recalculation yielded a pooled RR of 1.04 (95% CI 0.97–1.12) per drink.
Authors' conclusion	Alcohol consumption constitutes an independent risk factor for incidence of CAP. A monotonic dose–response relationship was found, and the RR for people with AUD was greater than eightfold.	
Reviewer's notes	No evidence of publication bias Random effects was used despite reporting I2=0.0% Age of participants in included studies not reported. 3 studies adjusted for age. All included studies adjusted for confounders (different variables) Cohort and case-control meta-analysed together. Narrow confidence intervals. Includes a large cohort study (104491)	

Table 49: AMSTAR assessment for Samokhvalov 2010

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies list not provided.
6	Were the characteristics of the included studies provided? [f]	Yes	Age not stated.
7	Was the scientific quality of the included studies assessed and documented? [g]	No	No mention of quality assessment.
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Samokhvalov 2015

Table 50: Data extraction for Samokhvalov 2015

General information	Systematic Review	Yes
	Title	Alcohol Consumption as a Risk Factor for Acute and Chronic Pancreatitis: A Systematic Review and a Series of Meta-analyses
	Country of origin	SR: Canada
	Source of funding	The work was financially supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (R21AA023521) to the last author.
	Possible conflicts of interest (for study authors or translators)	MR and JR report grants from the National Institutes of Health (NIH), National Institute on Alcohol Abuse and Alcoholism (NIAAA, R21AA023521), during the conduct of the study. AVS has no conflict of interest.
AMSTAR Rating		3
Characteristics of review and included primary studies	Aim/objectives of systematic review	The goal of the present systematic review and series of meta-analyses was to examine the association between alcohol consumption and risk of different types of pancreatitis (acute and chronic) by sex, including but not limited to analyses of potential threshold effects.
	Search Methods	OVID Medline, Embase, PsycINFO, PubMed, Scopus and Web of Science databases January 2009 and May 2015 The search was conducted using a combination of alcohol

		consumption related terms (“ethanol*”, “alcohol*”, “drink*”) and the term “pancreat*” as subject terms (descriptors).
	Level of evidence (lowest identified)	Level IV
	Study types identified	Case-control Cohort
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	NR
	Inclusion criteria	1) be of cohort or case–control study design; 2) have a control group of abstainers; 3) report relative risks (RR), odds ratios (OR), hazard ratios (HR), or contain data sufficient for their calculation; 4) have acute or chronic pancreatitis as an endpoint; and 5) include two or more categories of level of alcohol consumption in comparison to abstainers.
	Exclusion criteria	1) were of cross-sectional design; 2) did not have enough information to calculate a risk estimate; 3) reported only on alcoholic pancreatitis (alcohol-induced acute or chronic pancreatitis, K85.2 or K86.0); and 4) were not published as full reports (e.g. conference abstracts) or contained partial or incomplete data.
Exposure	Definition	two or more categories of level of alcohol consumption
	Method of measurement	NR
	Reference category	abstainers
	Statistical approach	We converted alcohol intake into average grams of pure alcohol per day (g/day) using the midpoints (mean) of reported drinking group categories. The midpoint for open-ended categories was calculated by adding 75% of the preceding category's range to the lower bound of the open-ended category. We used reported conversion factors when standard drinks were the unit of measurement.
Results: (per outcome)	Definition of outcome	Diagnoses of acute (AP) or chronic pancreatitis (CP)
	Method of measurement	International Classification of Disease (ICD) codes
	No. of studies and participants analysed by type of study	Seven studies with 157,026 participants and 3618 cases of pancreatitis
	No. of studies and participants excluded or missing (with reasons) by type of study	1757 at title/abstract screen 70 at full text (53 not original, 3 not enough data to calculate risk estimate, 2 duplicates, 1 pancreatitis etiology, 10 exposure not alcohol levels, 1 no control)
	Statistical method of analysis	random-effect models for categorical meta-analysis multivariable meta-regression models
	Significance/direction	a dose-response relationship between alcohol consumption and pancreatitis
	Heterogeneity	Between-study heterogeneity was low to moderate in analyses on AP among women, and moderate to high for CP and AP among men.
	Results	For risk of chronic pancreatitis it reported 25g per day of alcohol RR=1.58 (95% CI 1.32-1.90) and that for 100g per day this increased to RR=6.29 (95% CI 3.04-13.02). There was no evidence of non-linearity for chronic pancreatitis (p=0.091). For acute pancreatitis there was a separate dose-response meta-analysis for men and women in which there was no evidence of non-linearity (p=0.396) but significant evidence of non-linearity for women (p<0.001). The categorical meta-analysis for acute pancreatitis <40g per day reported no difference in men RR=1.10 (95% CI 0.69-1.74) and a decreased risk for women RR=0.76 (95% CI 0.60-0.97) in comparison to abstainers.
Authors’ conclusion	The dose–response relationships between alcohol consumption and risk of pancreatitis were monotonic for CP and AP in men, and non-linear for AP in women. Alcohol consumption below 40	

	g/day was associated with reduced risk of AP in women. Alcohol consumption beyond this level was increasingly detrimental for any type of pancreatitis.
Reviewer's notes	

Table 51: AMSTAR assessment for Samokhvalov 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	No	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	No	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Stockwell 2016

Table 52: Data extraction for Stockwell 2016

General information	Systematic Review	Yes
	Title	Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality
	Country of origin	SR: Australia
	Source of funding	This study was funded by National Institutes of Health Award # 1RO1AAO19939-02.
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		8
Characteristics of review and included primary studies	Aim/objectives of systematic review	The purpose of this study was to determine whether misclassifying former and occasional drinkers as abstainers and other potentially confounding study characteristics underlie observed positive health outcomes for low volume drinkers in prospective studies of all-cause mortality.
	Search Methods	Identified all potentially relevant English-language articles published up to December 31, 2014, by searching PubMed (last searched February 25, 2015) and the Web of Science and through reference list cross-checking of previous meta-analyses. Keywords: Mortality OR death OR coronary heart disease OR coronary artery disease OR ischemic heart disease OR atherosclerotic heart disease] AND [alcohol OR consumption OR ethanol OR alcohol drinking] AND [cohort OR prospective OR longitudinal]
	Level of evidence (lowest identified)	Level II
	Study types identified	Cohort
	Quality of evidence evaluated and summary of RoB	Studies were classified according to the presence or absence of two key types of potential bias: (a) including former drinkers and/or (b) including

		occasional drinkers in the abstainer reference category. coded a drinking measure as "adequate" for the purpose of estimating average daily alcohol intake if both quantity and frequency of drinking were assessed for a period of at least 1 week.
	RoB tool used	No formal assessment used
	Inclusion criteria	Included studies were original English-language research articles published in the peer-reviewed literature that quantified the relationship between all-cause mortality and alcohol consumption among human populations in cohort studies. All genders, age groups, and subjects from any racial, ethnic, cultural, or religious groups were eligible for inclusion, regardless of geographic region.
	Exclusion criteria	Studies were excluded if all-cause mortality outcomes could not be separated from morbidity outcomes. Studies were also excluded if the sample was defined in terms of pre-existing illness or poor health status.
Exposure	Definition	mean daily alcohol consumption
	Method of measurement	Mean daily alcohol consumption in grams of ethanol assessed at baseline. When studies did not define the grams of alcohol per unit or drink, published sources for country-specific estimates of typical drink size were used.
	Reference category	Occasional drinkers or abstainers. When occasional drinkers were the reference category and risk for abstainers was independently assessed, risk values were recalculated with abstainers as the reference group
	Statistical approach	predetermined definition of "low-volume" drinking (up to 20 g of ethanol per day for both men and women) broad definition of "occasional drinking" as less than one drink per week, because few studies reported outcomes for drinking less than monthly.
Results: (per outcome)	Definition of outcome	All-cause mortality
	Method of measurement	Hazard ratios and rate ratio estimates of mortality in individual studies were used as the RR estimates. Where studies only reported mortality rates, these were converted to RR estimates
	No. of studies and participants analysed by type of study	87 prospective cohort studies
	No. of studies and participants excluded or missing (with reasons) by type of study	2422 not on outcome or exposure of interest 54 not original studies, only those with pre-existing disease, case-control, cross-sectional 88 combined morbidity and mortality, had no alcohol categories, sample had pre-existing conditions, duplicates
	Statistical method of analysis	Between-study heterogeneity of RRs using Cochran's Q and the I2 statistic. Publication bias was assessed first through visual inspection of the funnel plot of log-RR of all-cause mortality due to alcohol consumption against the inverse standard error of log-RR and also by Egger's linear regression method. Mixed regression analyses were performed in which drinking groups and control variables were treated as fixed effects with a random-intercept study effect Three separate meta-analytical approaches: effects of various abstainer biases controlled for by inclusion of covariates in all models, stratified meta-analyses were performed on four distinct subsets of studies grouped according to the number and type of abstainer biases present, modelled only studies that met stricter quality criteria.
	Significance/direction	There may be a decreased risk of all-cause mortality with low alcohol consumption, however the effect sizes for decreased risk are small and their clinical/public health significance is uncertain. The decrease is affected by a number of study design characteristics. Former drinkers and people consuming ≥65 g/day of alcohol are at increased risk of all all-cause mortality.
	Heterogeneity	Moderate to considerable heterogeneity detected There was significant heterogeneity across studies ($p < .001$) for all drinking categories using the Q statistic and with I2 estimates also all significant and above 50%.
	Results	All-cause mortality risk by level of alcohol intake with standard adjustments

		only for both precision and between-study variation in estimates: Compared with occasional drinkers, in this model abstainers were at significantly higher risk (RR = 1.19, 95% CI [1.12, 1.27], p < .0001), low-volume drinkers were not at significantly different risk (RR = 1.02, 95% CI [0.95, 1.10]), and all drinkers combined were at significantly higher risk (RR = 1.24, 95% CI [1.08, 1.42], p = .0133). RR means indicated a significant protective effect for both low-volume (RR = 0.86, 95% CI [0.83, 0.90], p < .0001) and occasional drinkers (RR = 0.84, 95% CI [0.79, 0.89], p < .0001). Significantly increased risk was evident for former (RR = 1.22, 95% CI [1.14, 1.31], p < .0001), high-volume (RR = 1.12, 95% CI [1.07, 1.17], p < .0001), and higher volume drinkers (RR = 1.29, 95% CI [1.22, 1.36], p < .0001). Pooled estimates of all-cause mortality after adjustment. no significant protection was estimated for occasional (RR = 0.95, 95% CI [0.85, 1.05]), low-volume (RR = 0.97, 95% CI [0.88, 1.07]), or medium-volume drinkers (RR =1.07, 95% CI [0.97, 1.18]). As controls for abstainer biases and key covariates are removed, the RR estimate changes from 0.97 (95% CI [0.88, 1.07]) down to 0.86 (95% CI [0.83, 0.90]). Meta-analysis of higher quality studies. Seven higher quality studies free from abstainer bias indicated no significantly altered risk of all-cause mortality for any drinking group with the exception of a raised risk for higher volume drinkers (RR = 1.58, 95% CI [1.05, 2.38], p = .0295). Sensitivity analysis that each excluded just one study at a time identified Friesema et al. (2007) as being highly influential. When this study was removed, all RR estimates increased with both former (RR = 1.31, 95% CI [1.11, 1.55], p = .0022) and medium-volume drinkers (RR = 1.29, 95% CI [1.06, 1.56], p = .0106) having significantly elevated all-cause mortality risk. The risk estimate for low-volume drinkers was close to unity (RR = 1.04, 95% CI [0.95, 1.15]).
Authors' conclusion	Estimates of mortality risk from alcohol are significantly altered by study design and characteristics. Meta-analyses adjusting for these factors find that low-volume alcohol consumption has no net mortality benefit compared with lifetime abstention or occasional drinking. These findings have implications for public policy, the formulation of low-risk drinking guidelines, and future research on alcohol and health.	
Reviewer's notes		

Table 53: AMSTAR assessment for Stockwell 2016

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	Excluded studies not provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Some factors considered but no formal quality assessment undertaken
8	Was the scientific quality of the included studies used appropriately in [h]	Yes	Taken into account study design characteristics in analysis
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Taylor 2012

Table 54: Data extraction form for Taylor 2012

General information		Systematic Review
	Title	The relationship between alcohol consumption and fatal motor vehicle injury: high risk at low alcohol levels
	Country of origin	SR = Canada. Included studies = US, Australia, NZ
	Source of funding	National Institute for Alcohol Abuse and Alcoholism (NIAAA)
	Possible conflicts of interest (for study authors or translators)	Not reported.
AMSTAR Rating		4
Characteristics of review and included primary studies	Aim/objectives of systematic review	This systematic review and meta-analysis will fill a much needed gap in the alcohol-injury literature by providing data that will enable the development of stable dose–response risk curves for alcohol consumption and MVA fatal injury where none currently exist.
	Search Methods	January 1, 1980, and December 31, 2010 Medline, EMBASE, CINAHL, PubMED, Google Scholar, CABS,WHOLIST, SIGLE,ETOH, Alcohol in Moderation, and ISI Web of Science It combined the search terms “alcohol” AND “case –control” OR “case–crossover” AND “risk” AND [“injury” OR specific outcomes: “motor vehicle accidents”] Full reference lists of selected articles and key reviews were hand-searched
	Level of evidence (lowest identified)	Level II-3
	Study types identified	Case–control
	Quality of evidence evaluated and summary of RoB	None
	RoB tool used	None
	Inclusion criteria	Full articles (excluded reviews, editorials, and letters) of human studies
	Exclusion criteria	1. No indication of any information pertaining to an association between alcohol and injury mortality. 2. The study was NOT a case–control or cohort. 3. Inappropriate exposure data: No dose–response information presented (e.g., “yes” vs. “no” alcohol consumption was unacceptable in this case). All studies included in this review used BAC as the main measure of acute alcohol consumption. 4. The article did not measure fatal MVA injury specifically or did not specify only fatal MVA injury. 5. Acute consumption immediately preceding the MVA fatal injury was not presented, for example, only average or some measure of usual consumption was used.
Results: (per outcome)	Definition of outcome	Broad definition of fatal injury.
	Method of measurement	All descriptors including qualitative, mainly from roadside accident data, medical record/coroner’s file review, or combination.
	No. of studies and participants analysed by type of study	5 Case–control
	No. of studies and participants excluded or missing (with reasons) by type of study	121 excluded for no indication of any useful information 62 excluded due to no measure of fatal injury 16 excluded due to inappropriate exposure data 44 excluded due to inappropriate exposure 9 excluded due to inappropriate outcome 5 excluded due to design issues i.e. case only design
	Statistical method of analysis	Fractional polynomial regression for dose-response analysis. Random effect model for meta-analysis. Post hoc sensitivity analysis for 6 Zador data sets separately compared to one aggregated. No significant difference and heterogeneity remained

		significant.
	Significance/direction	Alcohol consumption increases risk of MVA.
	Heterogeneity	Significant, I2 = 99.4%, p < 0.0001
	Results	Random effects meta-analysis: Odds increased by 1.74 (95% CI: 1.43–2.14) for every 0.02% increase in BAC. Dose-response: At a BAC of 0.5%, the maximum OR of alcohol-attributable fatal injury was 595.05 (95% CI: 223.5–1,584.0). At a BAC level of 0.02 (roughly the equivalent of 1 standard drink), this analysis estimated the OR to be 3.64 (95% CI: 3.37–3.94). At the legal limit of 0.08, the legal BAC limit in most countries, the OR was calculated to be 13.0 (95% CI: 11.1–15.2). At levels above 0.08, the curve started to get much steeper with exponentially larger increases in fatal motor vehicle injury risk at these levels.
Authors' conclusion	At all levels of consumption, the odds of dying in a motor vehicle crash were significantly higher than for zero alcohol consumption and were approximately 13 times higher at the current legal limit of BAC = 0.08.	
Reviewer's notes	Publication bias was detected by the Begg's (p = 0.421) and Egger's (p = 0.032) tests, but lower power when study numbers are low, as in this SR. Funnel plot showed scarcity of studies reporting lower or null effects.	

Table 55: AMSTAR assessment for Taylor 2012

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? a	No	
2	Was there duplicate study selection and data extraction? b	No	
3	Was a comprehensive literature search performed? c	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? d	Yes	
5	Was a list of studies (included and excluded) provided? e	No	Excluded studies list not provided.
6	Were the characteristics of the included studies provided? f	Yes	
7	Was the scientific quality of the included studies assessed and documented? g	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? h	No	
9	Were the methods used to combine the findings of studies appropriate? i	No	Heterogeneity was assessed and a random effects model used but given I2=99.4% the appropriateness of meta-analysing the studies is questionable. No discussion of the potential causes of the heterogeneity within the sub-groups of the included studies.
10	Was the likelihood of publication bias assessed? j	Yes	
11	Was the conflict of interest stated? k	No	

Wang 2013

Table 56: Data extraction for Wang 2013

General information	Systematic Review	Yes
	Title	A meta-analysis of alcohol consumption and the risk of gout
	Country of origin	SR: China
	Source of funding	Not stated
	Possible conflicts of interest (for study authors or translators)	Declared there were none.
AMSTAR Rating		
Characteristics of review and included primary studies	Aim/objectives of systematic review	To assess the effect of alcohol consumption on the risk of gout.
	Search Methods	

	Level of evidence (lowest identified)	
	Study types identified	
	Quality of evidence evaluated and summary of RoB	
	RoB tool used	None used
	Inclusion criteria	(1) case–control or cohort study published as an original study to evaluate the association between alcohol consumption and risk of gout (2) multivariate-adjusted relative risk (RR) with 95 % confidence interval (CI) was provided (3) non/occasional drinking as the reference category.
	Exclusion criteria	NR
Exposure	Definition	Alcohol
	Method of measurement	The daily amount of alcohol consumption was assigned to three levels: light (≤1 drink, i.e., ≤12.5 g), moderate (>1 to <3 drinks/day, i.e., 12.6–37.4 g), and heavy (≥3 drinks, i.e., ≥37.5 g)
	Reference category	Non/occasional alcohol drinking (occasional drinking not defined)
	Statistical approach	
Results: (per outcome)	Definition of outcome	Adjusted RR for liver cirrhosis – morbidity or mortality (unadjusted was also used)
	Method of measurement	NR
	No. of studies and participants analysed by type of study	
	No. of studies and participants excluded or missing (with reasons) by type of study	
	Statistical method of analysis	The DerSimonian and Laird random effects model was selected as the pooling method if substantial heterogeneity was present (I 2>50 %)
	Significance/direction	
	Heterogeneity	
	Results	
Authors' conclusion		
Reviewer's notes	Egger's test did not support the presence of publication bias	

Table 57: AMSTAR assessment for Wang 2013

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Wang 2016a

Table 58: Data extraction for Wang 2016a

General information	Systematic Review	Yes
	Title	A meta-analysis of alcohol consumption and thyroid cancer risk
	Country of origin	China
	Source of funding	NR
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		6
Characteristics of review and included primary studies	Aim/objectives of systematic review	To investigate the possible association of alcohol consumption and thyroid cancer risk
	Search Methods	PubMed and Embase from the beginning of indexing to August 2015 using free text. Reference lists of reviews and included studies were checked
	Level of evidence (lowest identified)	III-2
	Study types identified	prospective cohort studies and case-control studies
	Quality of evidence evaluated and summary of RoB	5 to 9 (median of 8)
	RoB tool used	Newcastle–Ottawa Scale
	Inclusion criteria	(1) cohort study or case-control study published as original articles; (2) evaluated the association of alcohol consumption and thyroid cancer incidence in general population; (3) provided the relative risk (RR)/odds ratio (OR)/hazard ratio (HR) and the corresponding 95% confidence interval (CI) or sufficient information to enable calculation.
	Exclusion criteria	Abstracts or unpublished reports were not considered for inclusion in the meta-analysis.
Exposure	Definition	grams of ethanol per day light drinker defined as ≤1 drink/day (≤12.5 g/day of ethanol) and moderate as >1 drinks/day (>12.5 g/day of ethanol)
	Method of measurement	defined one drink as 12.5g of ethanol, 1 ml of alcohol as 0.8 g and 1 ounce as 28g
	Reference category	non-drinkers (recalculated according to method of Orsini et al when not used)
	Statistical approach	random effects meta-analysis
Results: (per outcome)	Definition of outcome	Thyroid cancer incidence
	Method of measurement	NR
	No. of studies and participants analysed by type of study	7 cohorts and 17 case-control studies (9,990 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis and dose response analysis
	Significance/direction	Significant, inverse association
	Heterogeneity	Light: 59.7% Moderate: 0%
	Results	Light 0.81 (95% CI 0.70-0.93) Moderate 0.71 (95% CI 0.63-0.79) For the comparison drinker vs. non-drinker, RR was closer to null for cohort than case-control studies Cohort: 0.87 (0.78, 0.96) (n=7) Case-control: 0.75 (0.63, 0.89) (n=17)
Authors' conclusion	This meta-analysis confirmed an inverse association between alcohol consumption and thyroid cancer risk.	
Reviewer's notes		

Table 59 AMSTAR quality assessment for Wang 2016a

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	

2	Was there duplicate study selection and data extraction? [b]	Yes	Both for study selection and data extraction
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

Wang 2016b

Table 60 Data extraction form for Wang 2016b

General information	Systematic Review	Yes
	Title	Association between alcohol intake and the risk of pancreatic cancer: a dose–response meta-analysis of cohort studies
	Country of origin	China
	Source of funding	none received
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		7
Characteristics of review and included primary studies	Aim/objectives of systematic review	The purpose of this study was to summarize and examine the evidence regarding the association between alcohol intake and pancreatic cancer risk based on results from prospective cohort studies.
	Search Methods	PubMed, Embase, Ovid, and the Cochrane Library to Aug 2015 using MeSH terms and free text. Reference lists of reviews and included studies were checked Note that Ovid is a platform not a database, therefore there is an error in either the reporting or the conduct of the search.
	Level of evidence (lowest identified)	II
	Study types identified	prospective cohort studies
	Quality of evidence evaluated and summary of RoB	ranged from 6 to 9 (mean 7.6)
	RoB tool used	Newcastle–Ottawa Scale
	Inclusion criteria	A study was eligible for inclusion if the study had a prospective cohort design, the study investigated the association between alcohol intake and the risk of pancreatic cancer, and the authors reported effect estimates (risk ratio [RR] or hazard ratio [HR]) and 95 % confidence intervals (CIs) comparing different alcohol intake categories with the lowest alcohol intake category. no restrictions placed on language or publication status
	Exclusion criteria	NR
Exposure	Definition	light (0–12 g per day), moderate (≥12-24 g per day), or heavy alcohol (≥24 g per day) intake
	Method of measurement	Converted all measurements into grams per day and defined one drink as 12 g of alcohol intake. The value assigned to each alcohol intake category was the mid-point for closed categories and the median for open categories.
	Reference category	'lowest alcohol intake level'
	Statistical approach	categorical meta-analysis and dose response curve based on the correlated natural log of RRs or HRs across alcohol intake categories, and modelled

General information	Systematic Review	Yes
		alcohol intake by using restricted cubic splines with three knots at fixed percentiles of 10 %, 50 %, and 90 % of the distribution
Results: (per outcome)	Definition of outcome	Pancreatic cancer incidence
	Method of measurement	NR
	No. of studies and participants analysed by type of study	19 prospective studies consisting of 21 cohorts (11,846 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis and dose response analysis
	Significance/direction	Mixed
	Heterogeneity	Low: 0% Moderate: 0% Heavy: 14.5%
	Results	Low (RR, 0.97; 95 % CI, 0.89–1.05) Moderate (RR, 0.98; 95 % CI: 0.93–1.03); Heavy (RR, 1.15; 95 % CI: 1.06–1.25) no evidence for a potential nonlinear relationship between alcohol intake and the risk of pancreatic cancer (P = 0.0874), although alcohol intake greater than 15 g/day seemed to be associated with an increased risk of pancreatic cancer.
Authors' conclusion	Low-to-moderate alcohol intake was not significantly associated with the risk of pancreatic cancer, whereas high alcohol intake was associated with an increased risk of pancreatic cancer.	
Reviewer's notes		

Table 61 AMSTAR quality assessment for Wang 2016b

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	Duplicate search, data extraction and quality assessment
3	Was a comprehensive literature search performed? [c]	Yes	Note: states "OVID" as a database
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF 2015a

Table 62 Data extraction form for WCRF 2015a

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Liver Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest	Not stated

General	Systematic Review	Yes
	(for study authors or translators)	
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To summarize the evidence from prospective studies and clinical trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of liver cancer in men and women.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-March 31st 2013.
	Level of evidence (lowest identified)	II
	Study types identified	Prospective cohort studies and nested case-controls
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Have to present results on an exposure/intervention relevant to the review (list of headings and subheadings of exposures in Annex 2). • Must have as outcome of interest incidence or mortality of liver cancer (histological type not specified) or hepatocellular carcinoma. • Have to present results from an epidemiologic study in men and/or women of one of the following types: • Randomized controlled trial • Group randomized controlled trial (Community trial) • Prospective cohort study • Nested case-control study • Case-cohort study • Historical cohort study • Any publication date. The CUP team only have to search and extract data from articles included in Medline from January 1st 2006, closure date of the database for the Second Expert Report. All other articles are already in the database were extracted
	Exclusion criteria	Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	Liver cancer or hepatocellular carcinoma incidence and mortality
	Method of measurement	NR
	No. of studies and participants analysed by type of study	14 cohort studies (5,650 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	5 cohort studies excluded (only 2 categories, superseded, cumulative intake, no RR, SIR)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association
	Heterogeneity	I^2=64%, p<0.01
	Results	RR (10 gr ethanol/day) = 1.04 (95% CI: 1.02-1.06; I_2=64.0%, $P_{heterogeneity} \leq 0.01$)

General	Systematic Review	Yes
		Significant evidence of publication bias (Egger's test, p=0.001) There was no evidence of non-linearity (p nonlinearity test=0.25) Four studies reported the relative risk estimate for the comparison of past alcohol drinkers with never drinkers. The summary estimate for the four studies was 2.58 (95% CI= 1.76-3.77). Exclusion of former drinkers might have attenuated the association of alcohol with liver cancer in some studies.
Authors' conclusion	Consumption of alcoholic drinks is a convincing cause of liver cancer. This is based on evidence for alcohol intakes above about 45 grams per day (around 3 drinks a day)	
Reviewer's notes		

Table 63 AMSTAR quality assessment for WCRF 2015a

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	Data checked after first ten extractions. If no systematic errors then a 10% sample are checked.
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF 2015b

Table 64 Data extraction form for WCRF 2015b

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Stomach Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of stomach cancer in men and women.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-February 28th 2014.

	Level of evidence (lowest identified)	II
	Study types identified	Prospective cohort studies, nested case-controls, case-cohorts
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None

	Inclusion criteria	• Have to present results on an exposure/intervention relevant to the review. The detailed list of exposures/interventions is in Annex 2.
		• Must have as outcome of interest incidence or mortality of gastric (stomach) cancer, cardia or noncardia gastric cancers
		• Have to present results from an epidemiologic study in men and women of one of the following types
		  o Randomized controlled trial
		  o Group randomized controlled trial (Community trial)
		  o Prospective cohort study
		  o Nested case-control study
		  o Case-cohort study
		  o Historical cohort study
		• Have any publication date

	Exclusion criteria	• Studies with cases of different anatomical localisations in addition to gastric cancer. For instance, gastrointestinal cancer, gastro-oesophageal cancers, etc. • Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders). • Articles in foreign language if cannot be translated (excluding articles in Chinese, French, Italian, Spanish, Portuguese and Iranian because members in the review team can read these languages).
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	gastric (stomach) cancer, cardia or noncardia gastric cancers incidence and mortality
	Method of measurement	NR
	No. of studies and participants analysed by type of study	23 studies (20 prospective cohorts, 1 case-cohort, 2 nested case-control) n= 11,926 cases
	No. of studies and participants excluded or missing (with reasons) by type of study	7 studies excluded (only 2 categories, superseded, mean exposure only)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association at higher levels
	Heterogeneity	All included studies: I^2= 38.6%, 0.03 Gastric cardia: I^2= 0%, 0.49 Non-cardia gastric: I^2= 83.2%, <0.001
	Results	All included studies: RR (10 gr ethanol/day) = 1.02 (1.00-1.04) Omitting Lindblad, 2005 (extremely high alcohol levels/quality issues): 1.03 (95% CI=1.01-1.04) Gastric cardia: 1.01 (0.99-1.03) n=6 Non-cardia gastric: 1.03 (0.97-1.09) n=7 There was significant evidence of small study bias. Small studies with estimates below the average are missing. Non-linear analysis showed that, while the test for non-linearity was not significant (p = 0.32), the linear dose-response association was statistically significant at quantities of alcohol (expressed as grams of ethanol) of 45 grams consumed per day and above

Authors' conclusion	Overall, the evidence tended to show increased risk of stomach cancer with greater alcohol intake. The dose-response meta-analysis was statistically significant when one study with exceptionally high reported intakes of alcohol was excluded. Non-linear analysis showed that the dose-response association was significant at higher levels of alcohol intake (from 45 grams per day). Stratified analysis revealed significant increased risk in men, for incidence in men and in Asian studies. Highest versus lowest analysis stratified by smoking status showed significant increased risk in both smokers and nonsmokers. Results were consistent for cardia and non-cardia cancers. There is evidence of plausible mechanisms in humans. Greater consumption of alcoholic drinks is probably a cause of stomach cancer. This is based on evidence for intakes greater than 45 grams per day (about 3 drinks a day).
Reviewer's notes	No studies were adjusted for Helicobacter pylori infection

Table 65 AMSTAR quality assessment for WCRF/AICR 2015b

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF 2016

Table 66 Data extraction form for WCRF 2016

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Oesophageal Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of oesophageal cancer in men and women.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-February 28th 2014.
	Level of evidence (lowest identified)	II

	Study types identified	Prospective cohort studies and nested case-controls
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Must have as exposure/intervention: dietary patterns, foods, nutrients ±dietary, supplemental or both, diet biomarkers, indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, and breastfeeding. • Must have as outcome of interest incidence or mortality of oesophageal cancer • Included in Medline from January 1st 2006 • Have to present results from an epidemiologic study in men and/or women of one of the following types: o Randomized controlled trial o Group randomized controlled trial (Community trial) o Prospective cohort study o Nested case-control study o Case-cohort study o Historical cohort study • In individuals free of cancer at the moment of exposure assessment or intervention (except non melanoma skin cancer)
	Exclusion criteria	• Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders). • Articles in foreign language that cannot be translated (members in the review team can read Chinese, French, Italian, Spanish and Portuguese).
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	Oesophageal adenocarcinoma, squamous cell carcinoma or oesophageal cancer not specified incidence and mortality
	Method of measurement	NR
	No. of studies and participants analysed by type of study	15 cohort studies, 1 nested case-control, 1 case-cohort (6,618 cases) For adenocarcinoma: 4 prospective cohorts, 1 case-cohort and 1 nested case-control For squamous cell carcinoma: 4 prospective cohorts, 1 case-cohort and 1 nested case-control
	No. of studies and participants excluded or missing (with reasons) by type of study	6 cohort studies excluded (only 2 categories, superseded, combined cancer sites)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association
	Heterogeneity	Combined: I^2=95.3%, <0.001 Adenocarcinoma: I^2=0.7%, 0.41 Squamous cell carcinoma: I^2=95.0%, <0.001
	Results	Combined: RR (10 gr ethanol/day) = 1.24 (1.16-1.33) Adenocarcinoma: 1.00 (0.98-1.02) (when excluding study described below: RR = 0.99 (0.92, 1.06, I^2 = 20.3%, p = 0.285) Squamous cell carcinoma: 1.25 (1.12-1.41) (when excluding study described below: RR = 1.30 (1.24, 1.36, I^2 = 39.3%, p = 0.159) Heterogeneity remained unexplained in stratified analysis. Visual inspection of the forest plot indicates that a substantial part of heterogeneity on the analysis on SCC is due to one study which had a high risk of bias. All studies on oesophageal squamous cell carcinoma were adjusted for

		smoking and all studies on oesophageal adenocarcinoma, except one, were adjusted for BMI or WHR
Authors' conclusion	For oesophageal squamous cell carcinoma, the evidence was generally consistent and the dose response meta-analysis showed a significant increased risk with increasing alcohol consumption. Consumption of alcoholic drinks is a convincing cause of oesophageal squamous cell carcinoma. For oesophageal adenocarcinoma, the evidence for an association was considered to be limited, and no conclusion was possible.	
Reviewer's notes		

Table 67 AMSTAR quality assessment for WCRF 2016

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF/AICR 2010

Table 68 Data extraction form for WCRF/AICR 2010

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To summarize the evidence from prospective studies and clinical trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of colorectal cancer.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-December 2009.
	Level of evidence (lowest identified)	III-2
	Study types identified	Prospective and retrospective cohort, nested case-control

	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Have to be included in Medline from January 1st 2006. • Have to present results from an epidemiologic study of one of the following types: o Randomized controlled trial o Group randomized controlled trial (Community trial) o Prospective cohort study o Nested case-control study o Case-cohort study o Historical cohort study • Must have as outcome of interest, incidence of colorectal, colon or rectum cancers, or mortality for these cancers. • Have to present results on the relevant exposures • Published in English language
	Exclusion criteria	• Are out of the research topic • Studies focusing on pre-malignant colorectal conditions, for example colorectal adenomas (that will be the topic of a different review) • Do not report measure of association between the exposure and the risk of colorectal, colon or rectum cancers • The measure of the relationship between exposure and outcome is only the mean difference of exposure • Are supplement to the main manuscript (e.g. Authors" Reply). • Are published on-line as "Epub ahead of print" or "In Press". The data of these articles will be extracted after the definitive version is released. • Are not in English language
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: colorectal cancer	Definition of outcome	colorectal cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	8 studies in meta-analysis (7 prospective cohorts, 1 case-cohort, 5,261 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	7 studies excluded with reasons (component or earlier report of another study, mean exposure)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association.
	Heterogeneity	I^2=50.7%, p=0.05 Men: I^2=21.1%, p=0.27 Women: I^2=0.0%, p=0.62 Egger's Test: (p=0.89)
	Results	RR= 1.10, (95% CI = 1.06-1.13), for 10g/day increase Men: RR= 1.11(1.08-1.15) Women: RR= 1.07(0.98-1.17)
Results: colon cancer	Definition of outcome	colon cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	12 studies in meta-analysis (10 prospective cohorts, 1 case-cohort, 1 nested case-control, 7,782 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	11 studies excluded from meta-analysis with reasons (insufficient data, replaced by later study, 2 categories only, mean data)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in

		a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association.
	Heterogeneity	I^2 = 60.1%, p=<0.01 Men: I^2=62.4%, p=<0.01 Women: I^2=34.2%, p=0.16 geographical region was a significant source of heterogeneity (p=<0.001) and gender was close to statistical significance (p=0.07) Egger's Test: (p=0.07)
	Results	RR = 1.08(1.04-1.13), for 10g/day increase Men: RR= 1.10(1.06-1.14) Women: RR= 1.03(0.96-1.10)
Results: rectal cancer	Definition of outcome	rectal cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	11 studies (9 prospective cohorts, 1 case-cohort, 1 nested case-control) (3,584 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	8 studies excluded from meta-analysis with reasons (replaced by later study, insufficient data, 2 categories only, mean exposure)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association
	Heterogeneity	I^2=0.0%; p=0.64 Men: I^2= 6.1%; p=0.39 Women: I^2=0.0%; p=0.54 Egger's Test: (p=0.35)
	Results	RR 1.10(1.07-1.12) per 10g/day increase Men: RR 1.10(1.07-1.13) Women: RR 1.09(1.03-1.16)
Authors' conclusion	The overall summary RRs obtained from the updated meta-analysis are consistent to what was observed in the WCRF/AICR report in 2007. With more new cohorts included in the updated meta-analysis, relatively stronger associations were observed in women, however only the summary RR for rectal cancer was statistically significant. WCRF 2007 conclusions: There is ample and generally consistent evidence from cohort studies. A dose-response is apparent. There is evidence for plausible mechanisms. The evidence that consumption of more than 30g/day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing, and probably also in women.	
Reviewer's notes		

Table 69 AMSTAR quality assessment for WCRF/AICR 2010

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	Note that not all data is double checked, a 10% sample is.
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis

8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

Table 70 Data extraction form for WCRF/AICR 2013 (colorectal)

General information	Systematic Review	Yes
	Title	Diet, nutrition, physical activity and colorectal cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To summarize the evidence from prospective studies and clinical trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of colorectal cancer.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-December 2009.
	Level of evidence (lowest identified)	III-2
	Study types identified	Prospective and retrospective cohort, nested case-control
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Have to be included in Medline from January 1st 2006. • Have to present results from an epidemiologic study of one of the following types: o Randomized controlled trial o Group randomized controlled trial (Community trial) o Prospective cohort study o Nested case-control study o Case-cohort study o Historical cohort study • Must have as outcome of interest, incidence of colorectal, colon or rectum cancers, or mortality for these cancers. • Have to present results on the relevant exposures • Published in English language
	Exclusion criteria	• Are out of the research topic • Studies focusing on pre-malignant colorectal conditions, for example colorectal adenomas (that will be the topic of a different review) • Do not report measure of association between the exposure and the risk of colorectal, colon or rectum cancers • The measure of the relationship between exposure and outcome is only the mean difference of exposure • Are supplement to the main manuscript (e.g. Authors" Reply). • Are published on-line as "Epub ahead of print" or "In Press". The data of these articles will be extracted after the definitive version is released. • Are not in English language
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: colorectal cancer	Definition of outcome	colorectal cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	8 studies in meta-analysis (7 prospective cohorts, 1 case-cohort, 5,261 cases)
	No. of studies and	7 studies excluded with reasons (component or earlier report of another study,

General	Systematic Review	Yes
	participants excluded or missing (with reasons) by type of study	mean exposure)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association.
	Heterogeneity	I^2=50.7%, p=0.05 Men: I^2=21.1%, p=0.27 Women: I^2=0.0%, p=0.62 Egger's Test: (p=0.89)
	Results	RR= 1.10, (95% CI = 1.06-1.13), for 10g/day increase Men: RR= 1.11(1.08-1.15) Women: RR= 1.07(0.98-1.17)
Results: colon cancer	Definition of outcome	colon cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	12 studies in meta-analysis (10 prospective cohorts, 1 case-cohort, 1 nested case-control, 7,782 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	11 studies excluded from meta-analysis with reasons (insufficient data, replaced by later study, 2 categories only, mean data)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association.
	Heterogeneity	I^2 = 60.1%, p=<0.01 Men: I^2=62.4%, p=<0.01 Women: I^2=34.2%, p=0.16 geographical region was a significant source of heterogeneity (p=<0.001) and gender was close to statistical significance (p=0.07) Egger's Test: (p=0.07)
	Results	RR = 1.08(1.04-1.13), for 10g/day increase Men: RR= 1.10(1.06-1.14) Women: RR= 1.03(0.96-1.10)
Results: rectal cancer	Definition of outcome	rectal cancer
	Method of measurement	Incidence
	No. of studies and participants analysed by type of study	11 studies (9 prospective cohorts, 1 case-cohort, 1 nested case-control) (3,584 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	8 studies excluded from meta-analysis with reasons (replaced by later study, insufficient data, 2 categories only, mean exposure)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Significant, positive association
	Heterogeneity	I^2=0.0%; p=0.64 Men: I^2= 6.1%; p=0.39 Women: I^2=0.0%; p=0.54 Egger's Test: (p=0.35)
	Results	RR 1.10(1.07-1.12) per 10g/day increase Men: RR 1.10(1.07-1.13) Women: RR 1.09(1.03-1.16)

General	Systematic Review	Yes
Authors' conclusion	The overall summary RRs obtained from the updated meta-analysis are consistent to what was observed in the WCRF/AICR report in 2007. With more new cohorts included in the updated meta-analysis, relatively stronger associations were observed in women, however only the summary RR for rectal cancer was statistically significant. WCRF 2007 conclusions: There is ample and generally consistent evidence from cohort studies. A dose-response is apparent. There is evidence for plausible mechanisms. The evidence that consumption of more than 30g/day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing, and probably also in women.	
Reviewer's notes		

Table 71: AMSTAR quality assessment for WCRF/AICR 2013b

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	Note that not all data is double checked, a 10% sample is.
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF/AICR 2014a

Table 72 Data extraction form for WCRF/AICR 2014a

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Bladder Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To summarize the evidence from prospective studies and clinical trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of bladder cancer in men and women.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-July 31st 2013.
	Level of evidence (lowest	III-2

	identified)	
	Study types identified	Prospective cohort, retrospective cohort, nested case-control
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Have to present results on an exposure/intervention relevant to the review (list of headings and subheadings of exposures in Annex 2). • Must have as outcome of interest incidence of bladder cancer or mortality from bladder cancer, including studies of transitional cell carcinoma, squamous-cell carcinoma and adenocarcinoma. Histologically defined carcinoma in situ of the bladder will also be considered an outcome for this review. Studies that reports imprecise anatomical definitions of cancer sites that include bladder cancer, such as urological tract cancer, will be included, provided that they are of invasive carcinoma. • Have to present results from an epidemiologic study in men and women of one of the following types: o Randomized controlled trial o Group randomized controlled trial (Community trial) o Prospective cohort study o Nested case-control study o Case-cohort study o Historical cohort study • Have to be included in Medline from January 1st 2006 (closure date of the database for the Second Expert Report).
	Exclusion criteria	• Do not report measure of association between any of the relevant exposures and outcomes. • Focus on pre-malignant bladder cancer other than histologically defined carcinoma in situ of the bladder. • Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure, because the difference is not adjusted for main confounders. • Are supplement to the main manuscript (e.g. Authors' Reply). • Published abstracts
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	bladder cancer
	Method of measurement	Incidence/mortality
	No. of studies and participants analysed by type of study	7 studies (6 prospective cohort, 1 retrospective cohort), n=2,673 cases
	No. of studies and participants excluded or missing (with reasons) by type of study	3 (unadjusted results, only high vs low, insufficient information)
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Non-significant, no effect
	Heterogeneity	I^2=44.6%, p=0.09
	Results	RR 0.97 (0.91-1.04)
Authors' conclusion	The summary RR per 10g of ethanol per day was 0.97 (95% CI: 0.91-1.04, I^2=44.6%, $p_{heterogeneity}$=0.09, n=7) with evidence of publication bias (p Egger's test =0.02. The smaller study reported a stronger positive association compared to the other studies. There was no evidence of nonlinearity (p=0.99).	
Reviewer's notes		

Table 73 AMSTAR quality assessment for WCRF/AICR 2013

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	Note that not all data is double checked. All data during first year of project double checked and then a 10% sample.
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

WCRF/AICR 2014b

Table 74 Data extraction form for WCRF/AICR 2014b

General information	Systematic Review	Yes
	Title	The Associations between Food, Nutrition and Physical Activity and the Risk of Gallbladder Cancer
	Country of origin	UK
	Source of funding	World Cancer Research Fund (WCRF)
	Possible conflicts of interest (for study authors or translators)	Not stated
AMSTAR Rating		7/11
Characteristics of review and included primary studies	Aim/objectives of systematic review	To summarize the evidence from prospective studies and clinical trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of gallbladder cancer in men and women.
	Search Methods	Medline search using MESH headings and free text without language restrictions. Hand search of retrieved studies. Search period January 1st 2006-March 31st 2013.
	Level of evidence (lowest identified)	II
	Study types identified	Prospective cohort
	Quality of evidence evaluated and summary of RoB	Sensitivity analysis for quality indicators (not reported for alcohol)
	RoB tool used	None
	Inclusion criteria	• Have to present results on an exposure/intervention relevant to the review (list of headings and subheadings of exposures in Annex 2). • Must have as outcome of interest incidence or mortality of gallbladder cancer. • Have to present results from an epidemiologic study in men and women of one of the following types: o Randomized controlled trial o Group randomized controlled trial (Community trial)

		○ Prospective cohort study ○ Nested case-control study ○ Case-cohort study ○ Historical cohort study • Have to be included in Medline from January 1st 2006 (closure date of the database for the Second Expert Report).
	Exclusion criteria	• Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
Exposure	Definition	Alcohol (as ethanol) 10g/day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range.
	Reference category	NR
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	gallbladder cancer
	Method of measurement	Incidence/mortality
	No. of studies and participants analysed by type of study	3 studies in meta-analysis (417 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	None
	Statistical method of analysis	study specific log odds ratios per unit increase in exposure were combined in a random effect model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model
	Significance/direction	Non-significant, no effect
	Heterogeneity	I^2=26.2%, p=0.25
	Results	RR 1.07 (0.98-1.17)
Authors' conclusion	The summary RR per 10 g/d was 1.07 (95% CI: 0.98-1.17; I^2=26.2%, $P_{heterogeneity}$ =0.25) for the three studies combined. There was no indication of publication bias with Egger's test (p=0.93).	
Reviewer's notes		

Table 75 AMSTAR quality assessment for WCRF/AICR 2015a

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	No	Only searched PubMed plus hand search. Justified in protocol and review, as prior work has demonstrated search other databases to not be cost-effective.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	Grey literature excluded. Searched trials registries for ongoing trials.
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	Undertaken in sensitivity analysis
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

Xu 2015

Table 76 Data extraction form for Xu 2015

General information	Systematic Review	Yes
	Title	Does beer, wine or liquor consumption correlate with the risk of renal cell carcinoma? A dose-response meta-analysis of prospective cohort studies
	Country of origin	China
	Source of funding	National Key Clinical Specialty Construction Project of China, Key Medical Disciplines of Zhejiang Province, Health Sector Scientific Research Special Project, Combination of Traditional Chinese and Western Medicine Key Disciplines of Zhejiang Province, Zhejiang Province Key Project of Science and Technology, National Natural Science Foundation of China, Scientific Research Foundation of the Ministry of Public Health of China .
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		9
Characteristics of review and included primary studies	Aim/objectives of systematic review	To update evidence on the association between alcohol consumption and renal cell carcinoma risk, and to quantify the sex-specific and beverage-specific dose-response relationships
	Search Methods	PubMed and EMBASE databases from to February 21, 2015 using free text. Reference lists of reviews and included studies were checked and grey literature searched
	Level of evidence (lowest identified)	III-2
	Study types identified	Cohort studies
	Quality of evidence evaluated and summary of RoB	Ranged from 6 to 9 (with a mean of 7.5)
	RoB tool used	Newcastle–Ottawa Scale
	Inclusion criteria	(i) cohort or nested case–control study conducted on the general population; (ii) one of the exposures was alcohol drinking; (iii) one of the outcomes was RCC risk; and (iv) studies reported risk estimates with their 95% confidence intervals (CIs), or data to calculate them.
	Exclusion criteria	Studies on special populations (e.g., cohorts of alcoholics) were not included
Exposure	Definition	Alcohol as grams per day Alcohol drinking were classified into three levels as light, moderate, and heavy drinking, which were defined as ethanol intake of <12.5 g/day (<1 drink/day), 12.5–37.5 g/day (2–3 drinks/day), and >37.5 g/day (>3 drinks/day), respectively.
	Method of measurement	using the following equivalencies: 1 ml of alcohol as 0.8 g of ethanol, one drink as 12.5 g, and 1 ounce as 28 g
	Reference category	non-drinker/occasional drinkers
	Statistical approach	categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	renal cell cancer/kidney cancer incidence and mortality
	Method of measurement	NR
	No. of studies and participants analysed by type of study	seven independent cohort studies and one pooled analysis of 12 cohort studies, 5,503 RCC cases
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis and dose response meta-analysis
	Significance/direction	Significant, inverse association
	Heterogeneity	Light: 45.2% Moderate: 45.1%

		Heavy: 74.8%
	Results	Light consumption: 0.92 (95% CI 0.83–1.01, 6 studies) Moderate consumption: 0.75 (95% CI 0.66–0.86, 8 studies) Heavy consumption: 1.08 (95% CI 0.42–2.75, 3 studies) Dose response per 5g/day increment: RR = 0.94 (95% CI 0.92–0.95, 8 studies) Males per 5g/day: (RR = 0.95, 95% CI 0.93–0.97, six studies) Females per 5g/day: (RR = 0.91, 95% CI 0.88–0.94, five studies)
Authors' conclusion	The present meta-analysis summarized the evidence from all available prospective cohort studies and found a significant 25% decreased risk of RCC for moderate drinking (2–3 drinks/day), compared with non/occasional drinking. A slightly more beneficial effect was observed for females. The dose-response analysis showed that each 5 g/day increment of alcohol intake corresponded to a 5% decrease in risk of RCC for males and 9% for females.	
Reviewer's notes		

Table 77: AMSTAR quality assessment for Xu 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Can't answer	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Yan Hong 2015

Table 78 Data extraction form for Yan-Hong 2015

General information	Systematic Review	Yes
	Title	Association between alcohol consumption and the risk of ovarian cancer: a meta-analysis of prospective observational studies
	Country of origin	China
	Source of funding	NR
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		6
Characteristics of review and included primary studies	Aim/objectives of systematic review	The purpose of this study was to summarize the data from prospective cohort studies on the relationship between alcohol consumption and ovarian cancer using a meta-analytic approach.
	Search Methods	PubMed, EMBASE and Cochrane databases from to May, 2014 using free text. Reference lists of reviews and included studies were checked
	Level of evidence (lowest identified)	II
	Study types identified	prospective cohort studies
	Quality of evidence evaluated and summary of RoB	ranged from 5 to 9 (mean 7.4)
	RoB tool used	Newcastle–Ottawa Scale

General information	Systematic Review	Yes
	Inclusion criteria	(1) the study had a prospective design (prospective cohort or nested prospective case control study), (2) the study investigated the association between alcohol intake and the risk of ovarian cancer, and (3) the authors reported effect estimates (risk ratio [RR] or hazard ratio [HR]) and 95% confidence intervals (CIs) for comparisons between individuals with high alcohol consumption and individuals who did not consume alcohol.
	Exclusion criteria	case–control studies studies that were not published as full reports, which included conference abstracts and letters to the editor
Exposure	Definition	low alcohol intake (<15 g/day) moderate alcohol intake (15– 30 g/day) heavy alcohol intake (>30 g/d)
	Method of measurement	NR
	Reference category	non-drinker – not defined
	Statistical approach	categorical meta-analysis
Results: (per outcome)	Definition of outcome	ovarian cancer incidence
	Method of measurement	NR
	No. of studies and participants analysed by type of study	13 prospective cohorts (n=5,587 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis
	Significance/direction	Non-significant, no association
	Heterogeneity	Light: 0% Moderate: 24.4% Heavy: 0%
	Results	Light consumption: RR, 0.96; (95% CI, 0.93–1.00) Moderate consumption: RR 1.08; (95% CI, 0.92–1.27) Heavy consumption: RR, 0.99; (95% CI, 0.88–1.12)
Authors' conclusion	Our study suggests that alcohol intake is not associated with an increased risk of ovarian cancer.	
Reviewer's notes		

Table 79 AMSTAR quality assessment for Yan-Hong 2015

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	No	Duplicate search (though not explicitly stated the study selection was duplicated), but not data extraction
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

Yang 2016

Table 80: Data extraction for Yang 2016

General information	Systematic Review	Yes
	Title	Alcohol consumption and risk of coronary artery disease: A dose-response meta-analysis of prospective studies
	Country of origin	SR: China
	Source of funding	This work was supported by grants from the National Natural Science Foundation of China (No 81270255), the Project Funded by the Science and Technological Innovation Group of Jiangsu Higher Education Institution "Qing-Lan Project" (JX2161015030).
	Possible conflicts of interest (for study authors or translators)	The authors state no conflict of interests.
AMSTAR Rating		5
Characteristics of review and included primary studies	Aim/objectives of systematic review	Aimed to better quantify the association between alcohol consumption and the risk of CAD through a comprehensive systematic literature review and dose-response meta-analysis that can intuitively reflect the relationship between alcohol consumption and risk of CAD.
	Search Methods	PubMed database Inception to March 2015 "coronary artery disease", "coronary heart disease", "cardiovascular disease", "myocardial infarction" (MI), "ischemic heart disease" (IHD), "CAD", "IHD combined with alcohol consumption", "drink", "drinking", and "ethanol". reference lists of pertinent articles were reviewed
	Level of evidence (lowest identified)	Level II
	Study types identified	Prospective cohort
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	NR
	Inclusion criteria	(1) the study was prospective design; (2) the exposure was alcohol consumption; (3) the outcome was total CAD incidence (including MI, CAD, nonstroke cardiovascular disease, and other coronary events); (4) the population was free from CAD at baseline; and (5) relative risks (RRs) with 95% confidence intervals (CIs), adjusted for at least age, were reported.
	Exclusion criteria	NR
Exposure	Definition	Alcohol consumption
	Method of measurement	NR
	Reference category	Non-drinkers
	Statistical approach	Standardized alcohol consumption across studies using a common scale, i.e., alcoholic g/d to pool the study-specific RRs. When a study reported alcohol consumption in drinks/week, we converted the intake into g/d assuming that one drink contains 12 g of alcohol. For each study, we assigned the median or mean alcohol consumption for the category to each corresponding RR. When the median or mean consumption was not reported, we assigned the midpoint of the upper and lower boundaries in each category as the median consumption. If the upper boundary for the highest category was not provided, the midpoint of the category was set at 1.5 times the lower boundary. When the lowest category was open-ended, we set the lower boundary to zero. If the number of cases and person-years were not available, we used the relative risks comparing the highest versus lowest categories of alcohol intake to obtain a summary estimate.
Results: (per outcome)	Definition of outcome	CAD incidence (including MI, CAD, non-stroke cardiovascular disease, and other coronary events)
	Method of measurement	NR

	No. of studies and participants analysed by type of study	13 articles from 18 prospective cohort studies, n=214,340, cases=7756 CAD
	No. of studies and participants excluded or missing (with reasons) by type of study	Excluded articles (n = 4867) Title and/or abstract were not relevant to the inclusion and exclusion criteria Excluded articles (n = 33): Did not evaluate this association(n=20) Case-control studies (n = 6) Reported CAD mortality(n=3) Did not report RR and/or 95% CI(n=3) Conducted on the same study populations as other included studies (n = 1)
	Statistical method of analysis	Heterogeneity among studies was estimated by the Cochran Q test and I2 statistic.
	Significance/direction	decreased risk of coronary artery disease incidence in people who consume alcohol when compared to non-drinkers, except for no difference at 135/day
	Heterogeneity	low I2=28.5%
	Results	A dose-response analysis reported a nonlinear association between alcohol consumption and risk of CAD (Pnonlinearity<0.00). For 12g/day RR=0.75 (95% CI 0.70–0.80), for 24g/day RR=0.70 (95% CI 0.66–0.75), for 36g/day RR=0.69 (95% CI 0.64–0.75), for 60g/day RR=0.70 (95% CI 0.64–0.77), for 90 g/day RR=0.74 (95% CI 0.67–0.83), for 135g/day RR=0.83 (95% CI 0.67–1.04), when compared with non-drinkers.
Authors' conclusion	Alcohol consumption in moderation is associated with a reduced risk of CAD with 36 grams/d of alcohol conferring a lower risk than other levels.	
Reviewer's notes		

Table 81: AMSTAR assessment for Yang 2016

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in [h]	No	
9	Were the methods used to combine the findings of studies	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	Only stated for review authors

Zeisser 2013

Table 82 Data extraction form for Zeisser 2013

General information	Systematic Review	Yes
	Title	A Systematic Review and Meta-Analysis of Alcohol Consumption and Injury Risk as a Function of Study Design and Recall Period
	Country of origin	SR: Australia

	Source of funding	This research was funded by Australia's Ministerial Council on Drug Strategy (MCDS) as well as the Centre for Addictions Research of BC Endowment held by the University of Victoria.
	Possible conflicts of interest (for study authors or translators)	NR
AMSTAR Rating		7
Characteristics of review and included primary studies	Aim/objectives of systematic review	
	Search Methods	1970 to 2009 MEDLINE, PsychInfo, and online journals Key terms, using Boolean operators, were (i) emergency room/emergency department/accident and emergency and (ii) alcohol/drinking/alcohol drinking. The initial search string was as follows: "emergency room" OR "ER" OR "emergency department" OR "ED" OR "injury" AND "alcohol." Results were further refined to focus on injury. Reference lists from recent relevant publications. Internet search engines (Google and Google Scholar) and the National Drug Research Institute library were extensively searched to locate unpublished government reports and other information relevant to ED studies. Key national and international researchers were contacted to inquire of new or upcoming studies that could potentially be included.
	Level of evidence (lowest identified)	Level IV – case-crossover is not stated in NHMRC levels of evidence.
	Study types identified	Cohort, case-control, case-crossover
	Quality of evidence evaluated and summary of RoB	Considers study design
	RoB tool used	None used
	Inclusion criteria	Studies published in English. Published in peer-reviewed journals. Studies on humans and adults only. Injured samples must have been drawn specifically from ED populations, not the general population. Controlled study design, that is, either case–control or case-crossover. Measured self-reported alcohol use within 6 hours of the injury (not within 6 hours of ED presentation). For studies with overlapping data (e.g., Cherpitel, 1988, 1997; Cherpitel et al., 1993), we used the most recent results for a particular site using the largest pool of subjects, being careful to avoid duplication by excluding earlier sets of results.
	Exclusion criteria	Studies that reported results restricted to only 1 kind of injury, for example, sports or suicide. Studies that drew cases from the general population rather than from ED population
Exposure	Definition	Self-reported alcohol use within 6 hours of the injury
	Method of measurement	Self-reported alcohol use within the 6-hour period prior to injury (not within 6 hours of ED presentation)
	Reference category	Not drinking alcohol in the prior 6 hours to injury
	Statistical approach	NR
Results: (per outcome)	Definition of outcome	Injury
	Method of measurement	Broad, general definition without strict adherence to ICD codes or diagnostic criteria.
	No. of studies and participants analysed by type of study	9 Case-control, 5 Case-crossover, n cases=22,182
	No. of studies and participants excluded or missing (with reasons) by type of study	Non-peer reviewed excluded: n= 2486 Excluded animal studies, non-English, non-adult etc.: n = 34 Excluded after scanning abstracts for relevance: n=498 Excluded after reading full texts for relevance: n=20 Duplicates excluded: n= 3

		Excluded due to time period other than 6 hours: n = 4 Excluded due to poor choice of control group: n = 7 Excluded due to inappropriate injury category: n = 6
	Statistical method of analysis	Random-effects (RE) model Publication bias was assessed using funnel and precision plots and regression analysis. Meta-regression was conducted to estimate the impact of the moderator variables study design (e.g., case–control vs. case-crossover) and alcohol consumption recall period (usual frequency, "yesterday," or "last week") and to formally test whether there was evidence of different effects in these different subgroups of trials. If a study reports on more than one country then each country was considered separately.
	Significance/direction	Alcohol consumption 6 hours prior increases risk of injury
	Heterogeneity	A significant Q-statistic (Q(26) = 356, p = 0.000) indicated between-study heterogeneity. The results of metaregression by study design indicated that there was significant heterogeneity owing to study design (i.e., ED case–controls, population case–controls, and case-crossover designs) and alcohol consumption recall period (e.g., usual frequency, "yesterday," and "last week").
	Results	Females: 5 studies OR=2.285 (95% CI 1.361-3.836), p=0.002 Males: 6 studies OR=1.071 (95% CI 0.715-1.605), p=0.732 Overall: 11 studies OR= 2.242 (95% CI 1.618-3.106), p=0.000 N studies (results), OR, Lower 95%CI, Upper 95%CI All studies 14 (27) 2.799 2.214 3.538 By study design: Case-crossover 5 (13) 3.815 2.646 5.499 ED case–control 4 (4) 3.145 1.583 6.247 Population case–control 4 (4) 3.145 1.583 6.247 By recall period reported: Usual frequency 2 (10) 4.235 2.541 7.057 "Yesterday" or "Last week" 12 (17) 2.320 1.789 3.008
Authors' conclusion	Study design and alcohol consumption recall period have significant effects on effect size magnitude in estimating the risk of injury from alcohol consumption 6 hours prior to injury. For the "usual frequency" case-crossover design, significant moderator effects were found, resulting in overestimates of injury risk from alcohol. ED case-crossover designs tend to overestimate risk, and ED case–control designs tend to underestimate.	
Reviewer's notes	Recall period (from paper): In the case-crossover study, each case becomes his or her matched control. This is achieved by asking the injured patient (case) to recall alcohol consumption at the same time of day as the injury occurred the day before and/or the week before.	

Table 83 AMSTAR assessment for Zeisser 2013

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Yes	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	No	Only gender was stated if adjusted for, not all confounders or if an adjusted analysis was used.
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	Yes	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	

11	Was the conflict of interest stated? [k]	No	

Zhou 2016a

Table 84 Data extraction form for Zhou 2016a

General information	Systematic Review	Yes
	Title	Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta–analysis
	Country of origin	Canada
	Source of funding	US National Institutes of Health
	Possible conflicts of interest (for study authors or translators)	Stated no conflict for three authors. One author has received funding from the Swedish retail alcohol monopoly which has a mandate to limit the public health consequences of alcohol consumption.
AMSTAR Rating		5
Characteristics of review and included primary studies	Aim/objectives of systematic review	(i) to investigate the relationship between prostate cancer and alcohol consumption; and (ii) to examine whether estimates of this relationship may have been biased by drink
	Search Methods	Searched PubMed and Web of Science to 31 December, 2014 using MESH headings and free text. Reference lists of reviews and included studies were checked.
	Level of evidence (lowest identified)	III-3
	Study types identified	cohort studies, case-control studies
	Quality of evidence evaluated and summary of RoB	NR
	RoB tool used	None
	Inclusion criteria	(i) case–control and cohort studies evaluating the relationship between alcohol consumption and prostate cancer; (ii) original articles published in English up till December 2014; (iii) articles that reported findings in odds ratio, hazard ratio, incidence ratio or standardized mortality ratio; and (iv) articles reporting at least three levels of alcohol consumption with drinking amounts, including the reference level. Articles with no abstainer group or a lowest drinking level greater than 0.33g/d were excluded. Additionally, studies reporting total alcohol consumption were included while
	Exclusion criteria	Studies based on consumption of specific beverages only such as wine, whiskey, vodka, sake or hard liquors were excluded. narrative reviews, letters, editorials, commentaries, unpublished manuscripts, dissertations, government reports, books and book chapters, conference proceedings, meeting abstracts, lectures and address, and consensus development statement including guideline statements, were excluded.
Exposure	Definition	level of daily alcohol consumption in grams of ethanol assessed at baseline
	Method of measurement	Converted using 8 g/unit for the UK; 10 g/drink for Australia, Austria, France, Greece, Hungary, Ireland, Netherlands, New Zealand, Poland, Spain, Sweden; 11 g/drink for Finland; 12 g/drink for Denmark, Germany, Italy, South Africa and Switzerland; 13.45 g/drink for Canada; 14 g/ drink for US; 12.5 g/drink for China, 19.75 g/drink for Japan and 12 g/drink for other countries. We converted alcohol intake into grams per day using the mid–points of reported categories to estimate mean values. Following practice in other meta–analyses involving self–reported alcohol consumption, the open–ended top categories (e.g. 6+ drinks/day) were coded by adding three–quarters of the range of the next lowest category to the lower bound
	Reference category	non-drinkers or abstainers (explored this in analysis) Studies were classified according to the presence or absence of two types of potential abstainer group bias: (i) including former drinkers and/or (ii) including occasional drinkers in the abstainer reference category.

	Statistical approach	categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	mortality and/or morbidity from prostate cancer (ICD–9: 185 or ICD–10: C61)
	Method of measurement	NR
	No. of studies and participants analysed by type of study	16 prospective cohorts (n=40,301 cases), 1 retrospective cohort (n=145 cases), 5 hospital–based case–control (n=5,093 cases) and 5 population–based case–control studies (n=4,300 cases). Total of 27 studies (n=49,848 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Multivariate meta-regression
	Significance/direction	Significant, positive association
	Heterogeneity	Low volume (1.30-<25g/day): I2=10.66% Medium volume (25– < 45 g/day): I2=1.00% High volume (45– < 65 g/day): I2=13.38% Higher volume (65+ g/day): I2=19.94%
	Results	Unadjusted estimates: Low: 1.09 (1.03 – 1.16) Medium: 1.03 (0.93 – 1.14) High: 1.13 (0.98 – 1.30) Higher: 1.15 (1.01 – 1.13) Fully adjusted estimates*: Low: 1.08 (1.04 – 1.11) Medium: 1.07 (1.02 – 1.12) High: 1.14 (1.08 – 1.22) Higher: 1.18 (1.10 – 1.27) Adjusted estimates in studies free of former and occasional drinker bias: Low (n=6): 1.23 (1.05 – 1.45) Medium-high (n=3): 1.20 (1.00 – 1.43)
Authors' conclusion	Our study finds, for the first time, a significant dose–response relationship between level of alcohol intake and risk of prostate cancer starting with low volume consumption (>1.3, <24 g per day). This relationship is stronger in the relatively few studies free of former drinker misclassification error.	
Reviewer's notes	* adjusted for between-study variation, both former and occasional drinker biases, US/non-US study and control for smoking status in individual studies	

Table 85 AMSTAR quality assessment for Zhou 2016a

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	No	
2	Was there duplicate study selection and data extraction? [b]	Yes	Both for study selection and data extraction
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	No	
5	Was a list of studies (included and excluded) provided? [e]	No	
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	No	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	No	

Zhou 2016b

Table 86 Data extraction form for Zhou 2016b

General information	Systematic Review	Yes
	Title	Does alcohol consumption modify the risk of endometrial cancer? A dose-response meta-analysis of prospective studies
	Country of origin	China
	Source of funding	Instructional Science and Technology Program of Changde city
	Possible conflicts of interest (for study authors or translators)	Stated no conflict
AMSTAR Rating		9
Characteristics of review and included primary studies	Aim/objectives of systematic review	The purpose of this meta-analysis is to systematically analyse the effect of alcohol intake on endometrial cancer risk
	Search Methods	Searched PubMed, Embase, Cochrane library and China Biological Medicine databases to January 5, 2016 using MESH headings and free text. Reference lists of reviews and included studies were checked.
	Level of evidence (lowest identified)	II
	Study types identified	Prospective cohort studies
	Quality of evidence evaluated and summary of RoB	Ranged from six to eight (mean = 7.10). The most common reason for deduction was no reported follow-up rate
	RoB tool used	Newcastle–Ottawa Scale
	Inclusion criteria	(1) exposure: alcohol consumption; (2) outcome: endometrial cancer; (3) design: prospective study, including cohort and case-cohort studies; and (4) effect size: relative risk (RR) with 95% confidence intervals (CI) or sufficient data to perform the calculation
	Exclusion criteria	NR
Exposure	Definition	Alcohol as grams per day
	Method of measurement	Converted published measures to grams per day, used the mid-point of a range. Assumed 12g per standard drink.
	Reference category	non-drinkers
	Statistical approach	categorical and dose-response meta-analysis
Results: (per outcome)	Definition of outcome	endometrial cancer
	Method of measurement	NR
	No. of studies and participants analysed by type of study	10 studies (9 prospective cohorts and 1 case-cohort, 9,766 cases)
	No. of studies and participants excluded or missing (with reasons) by type of study	NR
	Statistical method of analysis	Random effects meta-analysis
	Significance/direction	Non-significant, no association
	Heterogeneity	Moderate consumption: I^2=39% Heavy consumption: I^2=64%
	Results	Moderate consumption: 0.95 (95% CI 0.89–1.01) Heavy consumption: 1.00 (95% CI 0.88–1.13) Not modified by other lifestyle factors or the characteristics of the study design and population. No significant associations were detected in dose-response meta-analysis.
Authors' conclusion	Alcohol intake is not associated with endometrial cancer regardless of the beverage choice and alcohol consumption level.	
Reviewer's notes		

Table 87 AMSTAR quality assessment for Zhou 2016b

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]	Yes	
2	Was there duplicate study selection and data extraction? [b]	Yes	duplicate extraction, not duplicate study

			selection
3	Was a comprehensive literature search performed? [c]	Yes	
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]	Can't answer	
5	Was a list of studies (included and excluded) provided? [e]	Yes	Reference to all studies excluded at full text provided
6	Were the characteristics of the included studies provided? [f]	Yes	
7	Was the scientific quality of the included studies assessed and documented? [g]	Yes	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]	No	
9	Were the methods used to combine the findings of studies appropriate? [i]	Yes	
10	Was the likelihood of publication bias assessed? [j]	Yes	
11	Was the conflict of interest stated? [k]	Yes	

Full Text Screening

Question 1

Injury to self

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Andreuccetti 2012	Specifically only in Latin America and the Caribbean, particularly to gain information for low- to middle-income countries	Alcohol consumption	Injury (ED setting)	No - Population not applicable to the Australian general population.	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Branas 2015	Adults	Alcohol consumption	Firearm violence	No	Meta-analysis RCTs	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Does not meet PEO criteria.
Carra 2014	People with bipolar disorder	Current or lifetime AUD	Suicide	No Cross-sectional Case-control	No. Incorrect exposure and includes cross-sectional studies.	N/A	N/A	N/A	N/A	N/A	N/A	Comorbid AUD and SUD in individuals with BD are significantly associated with suicide attempts.	Exclude. Doesn't meet PEO criteria.
Cherpitel 2007	Patients in the ED with injury.	Alcohol consumption	Injury	Yes	Not stated	2005	N/A (this outcome has an SR more recently published)	N/A (this outcome has an SR more recently published)	N/A (this outcome has an SR more recently published)	N/A (this outcome has an SR more recently published)	N/A (this outcome has an SR more recently published)	….injured patients more likely to be positive for BAC and report drinking prior to injury than non-injured, and with the magnitude of the association substantially increased for violence-related injuries compared to non-violence-related injuries.	Exclude. Zeisser 2013 has a more recent search date.

Chrcanovic 2012	General population	Risk factors (including alcohol)	Maxillofacial fractures	Yes	Not stated	2011	Yes	No	No	No	No	N/A. No synthesis or conclusion for alcohol.	Exclude. Minimum criteria not met.
Hawton 2013	People with depression	Risk factors including alcohol misuse - not on a single occasion	Suicide	Cohort Case-control	No	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Factors significantly associated with suicide were: ...misuse of alcohol and drugs (OR=2.17, 95% CI=1.77–2.66).	Exclude. Doesn't meet PEO criteria.
Kool 2009	25-60 year olds	Alcohol consumption - some acute, but others usual consumption	Unintentional falls	No. Incorrect exposure.	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Nunn 2016	Trauma patients who were evaluated for one or more admissions to a hospital or trauma centre	Patients with a positive blood alcohol concentration (BAC) or other evidence of alcohol use on admission. There was no comparator group of no alcohol.	Percentage of patients with trauma recidivism with BAC. Risk ratios not reported as not compared to non-drinkers.	No. Incorrect exposure, outcome reporting and study type.	Any peer-reviewed primary study of original data involving human participants, including cross-sectional	Dec-15	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	The proportion of trauma recidivists with evidence of alcohol use on admission ranged from 26.7% to 76.9% (median 46.4%). The aggregated sample produced a weighted estimate of 41.0% (1388/3386) for alcohol-related trauma recidivism.	Exclude. Does not meet PEO criteria.
Taylor 2010	Adults (not just in the ED)	Alcohol consumption	Injury	Yes	Case-crossover Case-control	Nov-08	Yes	Partial - age and sex not stated	No	Yes	Yes	The risk of injury increases non-linearly with increasing alcohol consumption. For motor vehicle accidents, the odds ratio increases by 1.24 (95% CI: 1.18–1.31) per 10-g in pure alcohol increase to 52.0 (95% CI: 34.50–78.28) at 120 g. For non-motor vehicle injury, the OR increases by 1.30 (95% CI: 1.26–1.34) to an OR of 24.2 at 140 g (95% CI: 16.2–36.2). Case–crossover studies of non-MVA injury result in overall higher risks than case–control studies and the per-drink	Exclude. Zeisser 2013 has a more recent search date and provides a more in depth analysis of potential biases.

												increase in odds of injury was highest for intentional injury, at 1.38 (95% CI: 1.22–1.55).	
Taylor 2012	General population	Alcohol consumption	Motor vehicle injury	Yes	Cohort Case-control	Dec-10	Yes	Yes	No	Yes	Yes	This study is able to definitively show and quantify, for the first time, the significantly increased OR for fatal motor vehicle injury.	Include
Zeisser 2013	Patients in the ED with injury.	Self-reported alcohol consumption within 6 hours of injury	Injury	Yes	Case-control Case-crossover	2009	Yes	No - age, sex, confounders not stated.	Partial	Yes	Yes	The overall odds of injury were 2.799 (2.214 to 3.538, p < 0.001).	Include

Acute cardiovascular events

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Mostofsky 2016	General population	Alcohol consumption in the week prior to the event	Ischemic stroke myocardial infarction hemorraghic stroke	Yes	Case-control Case-crossover	Mar-15	Partial - Keywords not stated	yes	Partial - some factors considered - no tool used	Yes	Yes	There appears to be a consistent finding of an immediately higher cardiovascular risk following any alcohol consumption, but, by 24 hours, only heavy alcohol intake conferred continued risk.	Include

Injury to others

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic	Criteria 3: Quality assessment of included studies in	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude

								review?	systematic review?				
Cafferky 2015	Adults married or cohabiting	Overtime not on a single drinking occasion	Domestic violence	No. Incorrect exposure.	NR	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Crane 2016	Male participants and target of aggression females	Drinking but only in a laboratory setting	Male-female violence	No. Incorrect exposure and study type included.	Experimental	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Devries 2014	15+ years	Overtime not on a single drinking occasion	Intimate partner violence	No. Incorrect exposure.	Longitudinal Cross-sectional	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Rotham 2012	11-21 year olds	Overtime not on a single drinking occasion	Domestic violence	No. Incorrect exposure.	Longitudinal Cross-sectional	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.
Smith-Marek 2016	Adults in intimate relationships	Alcohol consumption but not in a single episode	Intimate partner violence	No. Incorrect exposure.	NR	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO criteria.

Sexually transmitted diseases

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Baliunas 2010	People with newly diagnosed HIV infections.	Consumption; binge consumption; consumption prior to, or at the time of, sexual relations	HIV	Yes	Cohort Case-control Nested case-control	May-08	Yes	Yes	No	No	No. Not applicable to Australian context as developed and developing nations analysed together.	Overall alcohol consumption (any of the three types identified) increased the risk of HIV (RR 1.98, 95% CI 1.59–2.47).	Exclude. Not applicable to Australian context.
Claxton 2015	Adults from community or campus	Some report from a single session of drinking but the majority did not	Engagement in casual sexual relationships (not specifically unprotected sex)	No. Incorrect outcome.	Non-experimental	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Doesn't meet PEO criteria.
Rehm 2011	Adult sample from community or campus	Alcohol consumption measured by BAC	Intention to engage in unprotected sex	No. Incorrect outcome and study design included.	RCTs	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Doesn't meet PEO criteria.

Scott-Sheldon 2016	Sample from community or university	Alcohol consumption measured by BAC	Intention to engage in unprotected sexual behaviours	No. Incorrect outcome and study design included.	Experimental	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Doesn't meet PEO criteria.

Sexual function

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Cheng 2007	Men	Overtime not on a single drinking occasion	Erectile dysfunction	No. Incorrect exposure and study type included.	Cross-sectional	Apr-06	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	N/A (does not meet PEO criteria)	Exclude. Does not meet PEO/study type criteria.

Harmful drug alcohol interactions

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Baldacchino 2016	Accidental overdose	Ethanol (usually measured by BAC)	Opioid overdose	Yes	Cohort Case-control	2013	Partial - reference lists not checked	Partial - confounders not stated	No	Yes	Partial - No explanation as to why meta-analysis not undertaken.	Factors that were modestly described with increased acute risk of fatal opioid overdoses due to hypoxia and cardiotoxicity include multiple sedative use (opioids and alcohol)…	Exclude - Does not meet minimum criteria.

Acute exacerbation of a mental illness

Study	Population	Exposure	Outcome	Meets PEO /study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Cairns 2014	Adolescents	Only includes one study that looks at average amount of alcohol consumed in a single drinking episode. This was analysed together with other studies looking at binge drinking in the past year etc.	Depression	No	Prospective cohort Systematic reviews of prospective cohort studies	N/A (incorrect exposure and study type included)	N/A (incorrect exposure and study type included)	N/A (incorrect exposure and study type included)	N/A (incorrect exposure and study type included)	N/A (incorrect exposure and study type included)	N/A (incorrect exposure and study type included)	Based on four studies, each contributing one association, the consumption of greater quantities of alcohol during drinking episodes (i.e., bingeing) was associated with higher levels of depression, with a small but significant mean effect size, but substantial heterogeneity (I2=89.2%).	Exclude. Doesn't meet PEO criteria.

Question 2

Liver disease

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude?
Cao 2016	Yes	General population	Alcohol with a reference group of no alcohol	Fatty liver disease (not defined if NAFLD or alcoholic FLD)	RCT (did not include any) Cohort Cross-sectional Case-control	No	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	Exclude. PEO not met.
Rehm 2010a	Yes	General population	3 or more categories of alcohol consumption	Cirrhosis	Cohort Case-control	Yes	Jan-08	MEDLINE, EMBASE, CINAHL, PsychINFO, Web of Science, ETOH, Google Scholar	Partial - confounders and age not stated	No	Yes	Yes	Alcohol consumption had a significantly larger impact on mortality of liver	Include. Meets minimum criteria and only one identified on cirrhosis.

								Keywords but not mesh terms stated Reference lists checked					cirrhosis compared with morbidity. Also, the same amount of average consumption was related to a higher risk of liver cirrhosis in women than in men. Overall, end-point was an important source of heterogeneity among study results.	
Roerecke 2016	Yes	General population	Categories of alcohol consumption in relation to non-drinkers	Fatty liver disease (not defined if NAFLD or alcoholic FLD)	Cohort Cross-sectional	No	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	N/A (incorrect outcome and study type)	Exclude. Does not meet PEO.
Sookian 2014	No	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)

Cardiovascular disease

Stroke

Study	Systematic review?	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Chen 2014	Yes	General population	Risk factors - including alcohol	Stroke	Yes	Prospective cohort	May-13	Yes	Partial - confounders and age not stated	Yes Newcastle-Ottawa scale	Yes	No - alcohol yes versus no only	The results from the studies of Asian populations indicated that long-term alcohol consumption was also a risk factor for stroke, although this factor had no effect on the incidence of stroke	Exclude. Only reported alcohol drinking versus not drinking, no levels of alcohol consumption.

													in Western populations (Table 3). Prior studies have also produced controversial results with respect to the significance of this factor: certain studies have determined that heavy long-term alcohol consumption is a risk factor for stroke [88], but other studies have reached the opposite conclusion [89]. However, heavy long-term alcohol consumption is a risk factor for many chronic diseases, and therefore, limiting alcohol consumption may play an indirect role in preventing the incidence of stroke.	
Larsson 2016	Yes	General population	Alcohol consumption	Stroke - ischaemic, subarachnoid hemorrhage, intracerebral hemorrhage	Yes	Prospective cohort	Sep-16	Partial - only PubMed searched.	Yes	Yes Newcastle-Ottawa scale	Yes	Yes	Light and moderate alcohol consumption was inversely associated only with ischemic stroke, whereas heavy drinking was associated with increased risk of all stroke types with a stronger association for hemorrhagic strokes.	Include. Most recent search date.
Patra 2010	Yes	General population	Three or more categories of alcohol consumption compared to abstention	Stroke (HR, RR, OR) morbidity and mortality	No	Cohort Case-control Systematic review Meta-analysis	Jun-09	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Included systematic reviews and meta-analysis.
Ronksley 2011	Yes	General population	Alcohol intake compared to non-drinkers	Coronary Heart Disease (incidence and mortality) Cardiac	Yes	Prospective cohort	Sep-09	Yes	Partial - confounders not stated	Partial - considered follow-up length and confounding.	Yes	Yes	Light to moderate alcohol consumption is associated with a reduced risk of	Exclude. A systematic review with a more recent search date was

				mortality Stroke									multiple cardiovascular outcomes.	identified.
Yao 2016	Yes	General population	Alcohol consumption (by quantity)	Subarachnoid hemorrhage	Yes	Cohort Case-control	Jan-16	Yes	Yes	Yes Newcastle-Ottawa scale	Yes	Yes	No significant association between light-to-moderate alcohol consumption and SAH. Heavy alcohol consumption was found to be associated with an increased risk of SAH. Dose-response analysis showed evidence of a linear association (P=0.0125) between alcohol consumption and SAH.	Exclude. A systematic review with a more recent search date was identified.
Zhang 2014a	Yes	General population	Different categories versus low alcohol intake	Stroke - ischaemic, haemorrhagic, mortality	Yes	Prospective cohort Prospective nested case-control	Jul-13	Yes	Partial - confounders not stated	Yes Newcastle-Ottawa scale	Yes	Yes	Low alcohol intake is associated with a reduced risk of stroke morbidity and mortality, whereas heavy alcohol intake is associated with an increased risk of total stroke. The association between alcohol intake and stroke morbidity and mortality is J-shaped.	Exclude. A systematic review with a more recent search date was identified.
Zheng 2015	Yes	General population	Different doses of alcohol intake compared to lowest or non-drinking	Coronary Heart Disease Total mortality Cardiac death Stroke Ischemic stroke	Yes	Prospective cohort. Nested case-control.	Jun-14	Yes	Partial - confounders not stated for all studies	Yes Newcastle-Ottawa scale	Yes	Yes but the focus of this analysis was on women compared to men.	Only authors' conclusion for risk of women compared to men.	Exclude. Focus of the review was men compared to women and a systematic review with a more recent search date was identified.

Heart failure

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Larsson 2015	Yes	General population	At least 3 different non-overlapping levels of drinking categories	Heart failure	Prospective cohort	Yes	Sep-14	Partial - one database searched	Yes	No	Yes	Yes	Author's conclusion: Alcohol consumption in moderation is associated with a reduced risk of HF. The pooled adjusted RRs of HF were 0.85 [95% CI 0.78–0.93] for light to moderate alcohol consumption (<14 drinks/week) and 0.90 (95% CI 0.72–1.13) for high alcohol consumption (≥14 drinks/week) compared with non-drinkers.	Include. Meets minimum criteria and has the most recent search date.
Padilla 2010	Yes	General population	Alcohol consumption	Heart failure	Prospective cohort Case-control	Yes	Dec-09	Partial - one database searched	No	No	Yes	Yes	Author's conclusion: infrequent and light-to-moderate drinking is associated with a lower risk of heart failure. Compared with never drinkers, the pooled relative risks were 1.16 (95% CI, 0.90–1.51) for former drinkers, 0.90 (95% CI, 0.83–0.98), 0.80	Exclude. Does not meet minimum criteria. Another systematic review with a more recent search date was identified.

													(95% CI, 0.73–0.88), 0.78 (95% CI, 0.65–0.95), and 0.77 (95% CI, 0.63–0.95) for current drinkers of 0.1 to 0.9, 1 to 7, 8 to 14, and >14 drinks per week, respectively.	

Atrial fibrillation

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Kodama 2011	Yes	Population and hospital based	Alcohol consumption	Atrial fibrillation or atrial flutter	Cohort Case-control	Yes	Dec-09	Yes	Yes	No	Levels of alcohol consumption not defined but excluded alcohol 'yes' or 'no' studies	Yes	The pooled estimate of AF for the highest versus the lowest alcohol intake was 1.51 (95% confidence interval: 1.31 to 1.74). A linear regression model showed that the pooled estimate for an increment of 10 g per day alcohol intake was 1.08 (95% confidence interval: 1.05 to 1.10; R2 0.43, p 0.001). A spline regression model also indicated that the AF risk increased with increasing levels of alcohol consumption.	Exclude. Other systematic review identified with a more recent search date that limits studies to prospective cohort and includes large cohort study by Larsson 2014.

Larsson 2014	Yes	Population and hospital based	Alcohol consumption	Atrial fibrillation incidence or atrial flutter	Prospective cohort	Yes	Jan-10	Partial - searched PubMed only but keywords defined.	Yes	No	Yes (3 or more categories of alcohol consumption)	Yes	Alcohol consumption is positively associated with risk of AF. Even moderate consumption of alcohol, which lowers the risk of other cardiovascular diseases, seems to slightly increase the risk of AF.	Include.
Samokhvalov 2010b	Yes	Population and hospital based	Three or more categories of alcohol consumption compared to abstention	Atrial fibrillation morbidity	Cohort Case-control	Yes	Apr-09	Yes	Partial	No	Yes (3 or more categories of alcohol consumption)	Yes - but dose-response	Epidemiological criteria for causality were met to conclude a causal impact of alcohol consumption on the onset of AF with a monotonic dose–response relationship. However, the impact of light drinking is not clear.	Exclude. Other systematic review identified with a more recent search date that limits studies to prospective cohort and includes large cohort study by Larsson 2014.

Hypertension

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Briasoulis 2012	Yes	General population	Three or more categories of alcohol consumption	Hypertension	Prospective cohort	Yes	May-12	Yes	No- confounders not stated	No	Yes	Yes	Alcohol consumption in moderation is associated with a reduced risk of HF. The pooled adjusted RRs of HF were 0.85 [95% CI 0.78–0.93] for light to moderate alcohol consumption	Include. Only review identified that meets PEO criteria.

													(<14 drinks/week) and 0.90 (95% CI 0.72–1.13) for high alcohol consumption (≥14 drinks/week) compared with non-drinkers.	
Wang 2015	Yes	General population	Dietary patterns (including alcohol consumption but only heavy versus none)	Hypertension	Cohort Case-control Cross-sectional	No. Exposure is only heavy drinking versus not drinking.	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	N/A (does not meet PEO or study type criteria)	Exclude. Incorrect exposure.

Coronary heart disease

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2008	Yes	General population	Alcohol consumption compared to abstainers	Coronary Heart Disease incidence and mortality	Prospective cohort	Yes	2006	Partial - only searched Medline.	Yes	No	Yes	Yes	This meta-analysis suggests that binge and heavy irregular drinking modify the favourable effect of alcohol intake on the CHD risk. However, this conclusion should be taken with caution because of the small number of studies considered.	Exclude. A systematic review with a more recent search date was identified.
Kelso 2015	Yes	People with HIV	Alcohol use	Coronary Heart Disease	No - includes cross-sectional	No - includes cross-sectional in meta-analysis and population may not be applicable to Australian context.	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)

Mente 2009	Yes	General population	Dietary factors, including alcohol	Coronary Heart Disease	Cohort study or RCT (unclear is any included for alcohol as no list of included studies provided).	Only partially meets PEO.	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)	N/A (incorrect study type)
Roerecke 2010	Yes	General population	Irregular heavy drinking	Ischaemic heart disease (in irregular heavy drinkers) mortality or morbidity	Cohort Case-control	Yes	Jul-08	Yes	Yes	Partial - none but have stated why and included inclusion/exclusion criteria	Yes	Yes	In a random-effects model, the pooled relative risk of irregular heavy drinking occasions compared with regular moderate drinking was 1.45 (95% confidence interval: 1.24, 1.70), with significant between-study heterogeneity (I 2 ¼ 53.9%). Results were robust in several sensitivity analyses. The authors concluded that the cardioprotective effect of moderate alcohol consumption disappears when, on average, light to moderate drinking is mixed with irregular heavy drinking occasions.	Exclude. A systematic review with a more recent search date was identified.
Roerecke 2010	Yes	General population	Former drinkers	Ischaemic heart disease (in former drinkers) mortality or morbidity	Cohort Case-control	Yes	Apr-10	Yes	Partial - Sex and confounders adjusted for stated. Age not stated.	Partial - none but have stated why and included inclusion/exclusion criteria	Yes	Yes	Pooled estimates for the subset stratified by sex and endpoint showed a significantly increased risk among former drinkers compared with long-term abstainers for IHD mortality (among men; relative risk ¼ 1.25, 95% confidence interval: 1.15, 1.36; among women relative risk ¼ 1.54, 95% confidence interval: 1.17, 2.03). For IHD morbidity, the estimates for both sexes were close to	Exclude. A systematic review with a more recent search date was identified.

													unity and not statistically significant.	
Roerecke 2012	Yes	General population	Three categories of alcohol consumption, over more than 2 weeks, with a combination of usual frequency and volume or number of drinks within a given period.	Ischaemic heart disease (in average consumption drinkers) mortality or morbidity	Cohort Case-control	Yes	Apr-10	Medline, EMBASE, Web of Science searched. Reference lists searched Comprehensive list of free-text keywords and subject headings	Partial - Sex and confounders adjusted for stated. Age not stated.	Partial - none but have stated why and included inclusion/exclusion criteria	Yes	Yes	A cardioprotective association between alcohol use and ischaemic heart disease cannot be assumed for all drinkers, even at low levels of intake. Although some form of a cardioprotective association was confirmed in all strata, substantial heterogeneity across studies remained unexplained and confidence intervals were relatively wide, in particular for average consumption of 1–2 drinks/day.	Exclude. A systematic review with a more recent search date was identified.
Roerecke 2014a and Roerecke 2014b	Yes	Chronic heavy drinkers in comparison to abstainers and the general population	Chronic heavy drinking >60g a day or AUD and current or lifetime abstainers	Ischaemic heart disease (in chronic heavy drinkers) mortality or morbidity	Prospective or historical cohort Case-control	Yes	Mar-14	Multiple databases searched Reference lists searched Search terms not comprehensive and MESH terms/search strategy not stated	Yes	Partial - none but have stated why and included inclusion/exclusion criteria	Yes	Yes	There is no systematic evidence for a protective association from any type of chronic heavy drinking on IHD risk. Patients with AUD were at higher risk for IHD mortality, but better quality evidence is needed with regard to potential confounding.	Exclude. A systematic review with a more recent search date was identified.
Ronksley 2011	Yes	General population	Alcohol intake compared to non-drinkers	Coronary Heart Disease Cardiac mortality Stroke (incidence and mortality)	Prospective cohort	Yes	Sep-09	Yes	Partial - confounders not stated	Partial - considered follow-up length and confounding.	Yes	Yes	Light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes.	Exclude. A systematic review with a more recent search date was identified.

Yang 2016	Yes	General population	Alcohol consumption	Coronary Heart Disease (incidence only)	Prospective cohort	Yes	Mar-15	Partial - only searched Medline.	Partial - no age.	No	Yes	Yes	Alcohol consumption in moderation is associated with a reduced risk of CAD with 36 grams/d of alcohol conferring a lower risk than other levels.	Exclude. A systematic review with a more recent search date was identified.
Zhang 2015	Yes	General population	Dietary factors, including alcohol (different alcohol consumption categories)	Coronary Heart Disease incidence and mortality	Cohort Case-control	Yes	Apr-15	Yes	No	NOS but results not reported (just mentions they are high quality)	Yes	Partial - sensitivity analysis not applicable - focusing on western-type diet and removing non-Western studies. Only looked at one category compared to none.	Evidence of a decreased risk of CHD in the moderate drinking compared with non-drinking category intake of the alcohol consumption levels (OR = 0.68; 95% CI: 0.59, 0.78; p < 0.00001)	Exclude. While this study had the most recent search date, its focus was not only on alcohol and the analysis was not as in-depth as others identified. There was no dose response and only moderate drinking compared to not drinking was analysed.
Zheng 2015	Yes	General population (focusing on men compared to women)	Different doses of alcohol intake compared to lowest or non-drinking	Coronary Heart Disease Total mortality Cardiac death Stroke Ischemic stroke (incidence and mortality)	Prospective cohort. Nested case-control.	Yes	Jun-14	Yes	Partial - confounders not stated for all studies	Yes Newcastle-Ottawa scale	Yes	No. Focus was on men compared to women.	The pooled RRR (female to male) of low alcohol intake (<15 g/day) versus the lowest alcohol or no alcohol intake was 1.01 (95 % CI: 0.84–1.21; P = 0.947; with no evidence of heterogeneity among included studies . Furthermore, the pooled RRR (female to male) was 0.96 (95 % CI: 0.75–1.23; P = 0.772;) for moderate alcohol intake (15–30 g/day). There was a significant heterogeneity among the included studies (I2 = 40.7 %; P = 0.096). Finally, the pooled RRR (female to male) was reduced by 10 %	Exclude. Focus was on men compared to women. A systematic review with a more recent search date was identified.

													(RRR, 0.90; 95 % CI: 0.66–1.22; P = 0.503; with moderate heterogeneity for heavy alcohol intake (>30 g/day), but this reduction was not statistically significant.	

Other

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Chiva-Blanch 2013	No	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)
Costanzo 2011	Yes	Patients with a history of CVD, diabetes and hypertension	Not specified	Vascular mortality & mortality from any cause	No	No	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	Exclude. Incorrect population
Djousse 2008	No	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)
Huang 2014	Yes	People with hypertension (not a predefined subgroup)	Alcohol consumption	Coronary Heart Disease Mortality Cardiac disease Stroke Ischemic stroke	Prospective cohort	No - not a pre-specified subgroup.	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	N/A (incorrect population)	Exclude. Incorrect population
Lippi 2015	Yes	General population	Alcohol consumption	Venous thromboembolism	Cohort Case-control Cross-sectional	Partial	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	No. No meta-analysis and no justification.	N/A (insufficient methods of analysis)	Exclude. Methods of analysis insufficient.

All-cause mortality

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Jayasekara 2014	General population	Alcohol consumption over time	All-cause mortality	Yes	Cohort	Aug-12	Yes	Yes	No	Yes	Yes	For men, there was weak evidence of lower mortality risk with low levels of alcohol intake over time but higher mortality risk for those with intakes over 40 g/day compared with abstainers using a random-effects model (P for nonlinearity = 0.02). The pooled relative risks were 0.90 (95% confidence interval: 0.81, 0.99) for 1–29 g/day, 1.19 (95% confidence interval: 0.89, 1.58) for 30–59 g/day, and 1.52 (95% confidence interval: 0.78, 2.98) for 60 or more g/day compared with abstention. There was moderate between-study heterogeneity but no evidence of publication bias. Studies including women were extremely scarce. Our findings include a curvilinear	Exclude. Systematic review with newer search date available.

												association between drinking over time and mortality risk for men overall and widespread disparity in methods used to capture exposure and report results.	
Laramee 2015	Alcohol dependency	Alcohol dependency compared to the general population	All-cause mortality	No - is not based on levels of alcohol exposure, only AUD compared to the general population (varying levels of alcohol intake)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)
Roerecke 2013	Alcohol use disorder	Alcohol dependency compared to the general population	All-cause mortality	No - is not based on levels of alcohol exposure, only AUD compared to the general population (varying levels of alcohol intake)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)

Roerecke 2013	Alcohol use disorder	Stratified by drinking levels (at least 3)	All-cause mortality	Yes	Cohort	May-12	Yes	Yes	No	Yes	Yes	In comparison to continued heavy drinking, a reduction below heavy levels of alcohol use (including abstention) was associated with a substantially reduced risk of mortality (random-effects pooled OR = 0.41; 95% CI, 0.34-0.50; P < .001). The OR was 0.35 (95% CI, 0.20-0.60; P < .001) for those who reached abstention and 0.61 (95% CI, 0.39-0.94; P = .026) for those who did not reach abstention but substantially reduced their consumption. The pooled OR for abstention compared to reduced consumption was 0.42 (95% CI, 0.19-0.92; P = .031). Meta-regression models did not reveal significant influences of study characteristics examined. Reduction of drinking in alcohol use disorders was associated with a marked reduction in mortality risk for those who reached abstinence or reduced drinking	Exclude. Systematic review with newer search date available.

												compared to continued heavy drinkers. Those who reached abstention showed the smallest mortality risk, lower than the risk for reduced consumption without abstinence.	
Silva 2014	Elderly	Social determinants	All-cause mortality	Partial	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	N/A (insufficient methods of analysis)	No - Only one study identified and insufficient level of analysis/discussion on alcohol	N/A (insufficient methods of analysis)	Exclude. Methods of analysis insufficient.
Stockwell 2015	General population	Alcohol consumption	All-cause mortality	Yes	Cohort	25-Feb-15	Yes	Yes	Partial	Yes	Yes	Estimates of mortality risk from alcohol are significantly altered by study design and characteristics. Meta-analyses adjusting for these factors find that low-volume alcohol consumption has no net mortality benefit compared with lifetime abstention or occasional drinking. These findings have implications for public policy, the formulation of	Include

												low-risk drinking guidelines, and future research on alcohol and health.	
Wang 2014	General population	Alcohol consumption	All-cause mortality (but focus on men versus women)	No - outcome focus is on risk for men compared to women.	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)	N/A (incorrect outcome)

Pancreatitis

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Alsamarrai 2012	Yes	General population	The reference group for alcohol use was alcohol nonusers, and the exposed groups were non-heavy (1–20 drinks per week) or heavy alcohol users (>20 drinks per week).	Pancreatic disease	Prospective cohorts only.	Yes	December 31, 2012	Yes	No - Confounders, age and sex not stated.	Yes. NOS.	Yes	Yes.	Compared with alcohol nonusers, the pooled RR of developing a pancreatic disease among alcohol users was 1.12 (95% CI, 0.94–1.33; P = .20, I2 = 76%). The pooled RRs for AP, CP, and PC were 1.33 (95% CI, 0.94–1.90; P ¼ .11, I2 = 55%), 1.23 (95% CI, 0.74–2.05; P = .43), and 1.01 (95% CI, 0.80–1.27; P = .92, I2 = 91%), respectively. Compared with alcohol nonusers, the pooled RR of a pancreatic disease among non-heavy alcohol users and heavy	Exclude. A newer SR Samokhvalov 2015 is available, which included a dose-response analysis and restricted included studies to two or more levels of alcohol consumption relative to abstainers.

													alcohol users was 0.96 (95% CI, 0.80–1.15; P = .69, I2 = 75%) and 1.37 (95% CI, 1.19–1.58; P < .01, I2 = 35%), respectively.	
Irving 2009	Yes	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	N/A Samokhvalov 2015 is an update of this review	We found a monotonic and approximately exponential dose-response relationship between average volume of alcohol consumption and pancreatitis. However, in a categorical analysis the lower drinking categories were not significantly elevated, with an apparent threshold of 4 drinks daily	Exclude. Samokhvalov 2015 is an update of this review
Samokhvalov 2015	Yes	General population	Two levels or more of alcohol consumption compared to abstainers	Acute and Chronic Pancreatitis	Cohort Case-control (specifically excluded cross-sectional)	Yes	May-15	Yes	No. Number of each sex not stated. Confounders stated. Age not stated for all studies.	No	Yes	Yes. Dose-response: cubic spline meta-regressions and categorical meta-analyses	The dose–response relationships between alcohol consumption and risk of pancreatitis were monotonic for CP and AP in men, and non-linear for AP in women. Alcohol consumption below 40 g/day was associated with reduced risk of AP in women. Alcohol consumption	Include

													beyond this level was increasingly detrimental for any type of pancreatitis.	

Diabetes and insulin resistance

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude?
Balianus 2009	Yes	General population	Alcohol consumption compared to current and lifetime abstainers	Diabetes	Cohort Case-control	Yes	31-Jan-08	Yes	Yes	No	No	Yes	Our analysis confirms previous research findings that moderate alcohol consumption is protective for type 2 diabetes in men and women.	Exclude. Systematic review with a more recent search date and that meets more of the protocol criteria identified.
Huang 2016	Yes	General population	Specific alcohol beverages including wine, beer, spirits.	Diabetes	Prospective cohort	No	Feb-16	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	Compared with beer or spirits, wine was associated with a more significant decreased risk of type 2 diabetes. The present study showed that wine might be more helpful for protection against type 2 diabetes than beer or spirits.	Exclude. Incorrect exposure.

Knott 2015	Yes	Adults aged 16 and over	Three or more categories of alcohol consumption, including never or non-drinking.	Diabetes	Cohort Case-control Case-cohort Nested case-control	Yes	18-Feb-14	Medline, EMBASE, CINAHL, ETOH. Reference lists searched Free-text keywords and combinations stated.	Yes	Yes Newcastle-Ottawa scale	Yes	Yes. Fractional polynomial regression	Reductions in risk among moderate alcohol drinkers may be confined to women and non-Asian populations. Although based on a minority of studies, there is also the possibility that reductions in risk may have been overestimated by studies using a referent group contaminated by less healthy former drinkers.	Include. Newest review that meets all criteria.
Li 2016	Yes	General population	Alcohol consumption compared to abstainers	Diabetes	Prospective cohort	Yes	24-Mar-15	Yes	Yes	Yes. NOS	Yes	No. Did not investigate heterogeneity sufficiently. Results for men and women are reported in the text, which it is unclear from the graphs how this result was determined.	Light and moderate alcohol consumption was associated with a lower risk of T2D, whereas heavy alcohol consumption was not related to the risk of T2D.	Exclude, due to methods of analysis.

Cancer

Bladder

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Alcohol was not significantly associated with the risk of adenocarcinoma of the bladder (19 studies). RR 0.99 (0.89-1.10) light, 1.01 (0.91-1.12) moderate, 0.95 (0.75-1.20) heavy consumption.	Exclude. Another SR with a more recent search date and meeting more criteria identified.
Mao 2010	General population	Alcohol consumption	Bladder cancer	Yes	Case-control or cohort studies	01-Dec-09	No Full terms not provided, unclear whether only searched PubMed	Yes	No	Yes	Partial No sensitivity analysis using adjusted vs. unadjusted estimates	The overall current literature on alcohol consumption and the risk of bladder cancer suggested no association, while the consumption of beer and wine was associated with reduced risk of bladder cancer.	Exclude. Another SR with a more recent search date and meeting more criteria identified.
Pelucchi 2009	General population	Alcohol and coffee consumption	Bladder cancer	Yes	Case-control or cohort studies	01-Aug-07	Partial Searched PubMed only	No	No	Yes	No	Epidemiological data on alcohol drinking and bladder cancer are suggestive of no association, although findings were not always consistent.	Exclude. Another SR with a more recent search date and meeting more criteria identified.
Pelucchi 2012	General population	Different levels of alcohol consumption	Bladder cancer	Yes	Case-control or cohort studies	01-Oct-10	Partial Searched PubMed only	Yes	No	Yes	Yes	Compared with non-drinkers, the pooled RRs of bladder cancer were 1.00 (0.92-1.09) for moderate and 1.02 (0.78-1.33) for heavy alcohol drinkers. When we excluded four studies that did not adjust for tobacco smoking, the corresponding estimates were 0.98 (0.89-1.07) and 0.97 (0.72-1.31). Provides definite evidence on the absence of any material association between alcohol drinking and bladder cancer risk, even at high levels of consumption.	Exclude. Another SR with a more recent search date and meeting more criteria identified. Same group as Bagnardi 2015.
WCRF 2015c	General population	All exposures related to food, nutrition and physical activity	Bladder cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	31-Jul-13	Partial Searched PubMed only (justified)	Yes	Partial Study quality considered in report	Yes	Yes		Include. Most recent search date.

Brain

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Alcohol was not significantly associated with the risk of brain cancer (6 studies.) RR 1.01 (0.86-1.18) light, 1.10 (0.84-1.43) moderate, 1.45 (0.69-3.08) heavy.	Include. Most recent search date that analysed by levels
Galeone 2013	General population	Alcohol consumption	Adult brain cancer	Yes	Case-control or cohort	01-Sep-11	Yes	Yes	No	Yes	Yes	Alcohol does not appear to be associated with adult brain cancer, though a potential effect of high doses deserves further study. Pooled RR 1.01 (0.81-1.25) moderate, 1.35 (0.85-2.15) heavy.	Exclude. Same group as Bagnardi

Qi 2014	General population	alcohol consumption	glioma	Yes	case-control or cohort design	08-Aug-13	Yes	Yes	Yes	Yes	No Only analysed by drinker vs non-drinker	Our results show no material association between alcohol consumption and risk of glioma. Combined RR for total alcohol drinkers versus non-drinkers was 0.96 (0.89-1.04).	Exclude. No levels of alcohol analysed.

Breast

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Albuquerque 2014	women	dietary pattern	Female breast cancer	Partial	epidemiological studies	01-Dec-12	Yes	Yes	No stated in methodology, but results not reported	Yes	No	Diets that include alcoholic beverages may be associated with increased risk	Exclude. SR identified that met more of the criteria. Methods of analysis means results cannot be reliably interpreted.
Bagnardi 2013	General population	Light drinkers (≤12.5 g or ≤21 drink) vs. non-drinkers	Oral cavity and pharynx, larynx, esophagus, liver, colorectum, breast	Partial	Case-control or cohort	01-Dec-10	Yes	Partial Included table of study characteristics but pooled by cancer site	No	Yes	Partial	Light drinking (up to 1 drink/day) was associated with female breast cancer (RR = 1.05, 95% CI: 1.02-1.08).	Exclude. SR identified that met more of the criteria. From Bagnardi group.

Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Summary relative risk of 1.04 (95% CI: 1.01-1.07, I2=63%) for light (≤12.5g per day) consumption, 1.23 (95% CI: 1.19-1.28, I2=54%) for moderate (≤50g per day) consumption and 1.61 (95% CI: 1.33-1.94, I2=10%) for heavy (>50g per day) alcohol consumption. Every category of alcohol consumption, from light to heavy drinking, was associated with an increased risk of cancer – in a dose-risk manner – of the female breast.	Exclude. SR identified that met more of the criteria.
Jayasekara 2016	General population	Alcohol consumption over time	Incidence of breast cancer	Partial	Cohort and case-control	01-Jan-15	Yes	Yes	No	Yes	Yes	A relatively weak, positive, non-linear dose response relationship between alcohol intake during lifetime and breast cancer incidence was shown. The pooled RR for highest versus lowest category of alcohol intake was 1.28 (95% CI: 1.07-1.52).	Exclude. Although this review had a more recent search date it did not undertake any quality assessment. The WCRF considered some elements of quality within the report.

Seitz 2012	General population	Alcohol consumption	Breast cancer	Yes	Case-control or cohort	01-Nov-11	Yes	No (might be in supp, can't locate)	No	Yes	Yes	A significant increase of the order of 4% in the risk of breast cancer is already present at intakes of up to one drink/day. Heavy alcohol consumption, defined as three or more drinks/day, is associated with an increased risk by 40-50%.	Exclude. SR identified that met more of the criteria. From Bagnardi group.
WCRF 2008	General population	All exposures related to food, nutrition and physical activity	Breast cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	01-Dec-07	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes	The summary estimate obtained in the meta-analysis of post-menopausal breast cancer was 1.08 (95% CI = 1.05-1.11) for 10g/day increase in alcohol consumption. There was no suggestion of excess heterogeneity between the studies (I2=21.0%, P=0.231) and no indication of any strong influence from each individual study on the summary estimate. The funnel plot did not suggest any publication bias. Overall, the categorical results are consistent with a positive significant association as shown in the forest plot of relative risks	Include. Although this review had the least recent search date (December 2007), it was of higher quality and either met or partially met all inclusion criteria, in comparison to the remaining reviews all of which failed to undertake any quality assessment. This review is currently being updated and the Continuous Update Project's independent Expert Panel will discuss the evidence in 2016.

												comparing highest versus lowest category of intake in each study. The meta-analysis of pre-menopausal breast cancer was not updated (5 studies: RR = 1.09, 95% CI = 1.01-1.17, with significant heterogeneity (I2 = 66%, possibly explained by differential adjustment for age, anthropometry and genetic factors).	
Zeisser 2014	General population (assumed)	Former drinkers (now abstainers), occasional drinkers (less than 1 drink per week), low-level drinkers (1 drink/month to 2 drinks/day), hazardous level drinkers (2 to 4 drinks/day), harmful-level drinkers (greater than 4 drinks/day)	Breast cancer	Yes	Hospital- or population case-control, and cohort studies	Dec-13	No - MEDLINE only	Partially - the purpose of this paper was to re-assess data analyses in light of misclassification errors. Potential confounders such as women at high-risk of developing breast cancer and co-morbidities not explored in this study	No	Yes	Authors used a mixed-effects model rather than fixed-effect model due to heterogeneity. A mixed-effect regression was also undertaken. The study assessed the impact of different drinker misclassification errors using revised thresholds for the "abstainer" group	"Unbiased estimates of the odds ratio (OR) for breast cancer was 1.011 (95% CI 0.891 to 1.148) among former drinkers (11 studies) and 1.034 (95% CI 1.0003 to 1.064) among occasional drinkers (17 studies)…In studies free from occasional drinker bias, the OR for breast cancer was 1.085 (95% CI 1.015 to 1.160) for low-level drinkers (17 studies), 1.374 (95% CI 1.319 to 1.431) for hazardous drinkers and 1.336 (95% CI 1.128 to 1.454) for harmful level drinkers (9 studies)"	Excluded superseded by WCRF paper

Cervical

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes		Include. Only SR that meets the minimum criteria.
Hjartaker 2010	General population	Alcohol consumption	Gynaecological cancers	Yes	Cohort and case-control	01-Mar-10	Partially Searched PubMed only	No	No	Yes	No	Overall, the body of evidence suggests a possible association between alcohol consumption and the risk of cervical cancer. However, it is possible that the positive relation observed in some of the studies is confounded by several risk factors.	Exclude. Doesn't meet the minimum criteria.

Colorectal

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Feng 2016	General population	Dietary pattern	Colorectal cancer	Partial	cohort, case-control and cross-sectional	01-Jun-15	Yes	Yes	Yes	Yes	No Not clear whether adjusted estimates used, no sensitivity analysis using adjusted vs.	There was an increased risk of colorectal cancer in the highest compared with the lowest category of	Exclude. Methods of analysis insufficient.

											unadjusted. Only highest vs. lowest levels of consumption.	'alcohol consumption' pattern (OR=1.44; CI:1.13-1.82)	
Jayasekara 2016	General population	Alcohol consumption over time	Incidence of breast, colorectal and upper aerodigestive tract cancer (oral cavity, pharynx, larynx or oesophagus, individually or combined)	Partial	Cohort and case-control	01-Jan-15	Yes	Yes	No	Yes	Yes	Pooled RR was 1.49 (95% CI: 1.27-1.74). Confirms a dose-dependent association with long term alcohol intake and colorectal cancer.	Exclude. Only partially met the PEO.
Wang 2015	General population	At least three categories of alcohol drinking	colorectal cancer	Yes	case-control, case-cohort or cohort	01-Jul-14	Partial years not specified, terms appear brief	Yes	No State that they have undertaken quality assessment, but not reported an inappropriate instrument	Yes	Partial No sensitivity analysis using adjusted vs. unadjusted estimates	The RRs were 1.07 (95% CI, 1.02-1.13), 1.23 (95% CI, 1.15-1.32) and 1.37 (95% CI, 1.26-1.49) for light (≤12.5 g/day), moderate (12.6 to 49.9 g/day) and heavy drinking (≥50 g/day), respectively. The risks were consistent in the subgroup analyses of sex and tumor site. This meta-analysis provides strong evidence for an	

												association between alcohol intake and colorectal cancer risk.	
Zhang 2015a	General population	Consumption of beer	colorectal cancer	No	Case-control or cohort	01-Jun-14							Exclude. Doesn't meet PEO.
Zhu 2014	General population	At least three categories of alcohol drinking	colorectal cancer	Yes	Case-control, nested case-control or cohort	01-Jan-14	No Searched PubMed only, terms brief, no mention of searching reference lists etc.	Yes	No State they used Newcastle-Ottawa scale but results not reported	Yes	Partial Not clear whether adjusted estimates used, not analysed in sensitivity analysis	The dose–response analysis demonstrated that for drinkers of 10, 25, 50 and 100 g/day alcohol consumption, the estimated RRs of CRA were 1.02 (95% CI 0.89–1.16), 1.06 (95% CI 0.92–1.20), 1.16 (95% CI 1.02–1.33) and 1.61 (95% CI 1.42–1.84) respectively, in comparison with non-/occasional drinkers. This study suggests that alcohol intake is related to a significant increase of risk for colorectal adenoma.	Exclude. Methods of analysis insufficient.

Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	The RRs were 0.99 (95% CI, 0.95-1.04), 1.17 (95% CI, 1.11-1.24) and 1.44 (95% CI, 1.25-1.65) for light (≤12.5 g/day), moderate (≥50 g/day) and heavy (>50g/day) consumption respectively. Moderate and heavy drinking, but not light drinking, was associated with an increased risk of cancer of the colorectum.	Exclude. Although this SR was newer, WCRF partially met more criteria than this SR.
Bagnardi 2013	General population	Light drinkers (≤12.5 g or ≤21 drink) vs. non-drinkers	Oral cavity and pharynx, larynx, esophagus, liver, colorectum, breast	Partial	Case-control or cohort	01-Dec-10	Yes	Partial Included table of study characteristics but pooled by cancer site	No	Yes	Yes	No significant association was observed between light drinking and cancer of the colorectum (RR= 0.99, 95% CI: 0.95-1.04).	Exclude. Older SR but same group as Bagnardi 2015
Magalhaes 2012	General population	Dietary pattern	colorectal cancer	Partial	Case-control or cohort	01-Aug-10	Yes (note alcohol was not used as a search term)	Might be in supplementary - can't access	No	No	No	'Drinker' characterized by high alcohol consumption: colon cancer (RR=0.96, 95% CI: 0.82-1.12,	Exclude. Doesn't meet minimum criteria.

												I(2)=0.6%); rectal cancer (RR=0.83, 95% CI: 0.47-1.45, I(2)=65.1%)	
Fedirko 2011	General population	At least three categories of alcohol exposure	colorectal cancer	Yes	observational epidemiological studies (case-control, case-cohort, cohort)	01-May-10	No PubMed only	Yes	No	Yes	Yes	The dose–risk analysis estimated RRs of 1.07 (95% CI 1.04–1.10), 1.38 (95% CI 1.28–1.50), and 1.82 (95% CI 1.41–2.35) for 10, 50, and 100 g/day of alcohol, respectively. This meta-analysis provides strong evidence for an association between alcohol drinking of >1 drink/ day and colorectal cancer risk.	Exclude. Older SR but same group as Bagnardi 2015
WCRF 2010	General population	All exposures related to food, nutrition and physical activity	colorectal cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	01-Dec-09	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes		Include. Met the minimum criteria and partially met the other criteria.

Huxley 2009	General population	Lifestyle risk factors	colorectal cancer incidence	Yes	prospective cohort studies	01-Jan-08	Yes	Yes	Partially Only included cohort design	Yes	No Only included highest vs. lowest	The risk of colorectal cancer was significantly associated with alcohol: individuals consuming the most alcohol had 60% greater risk of colorectal cancer compared with non- or light drinkers (relative risk 1.56, 95% CI 1.42–1.70).	Exclude. Methods of analysis insufficient.
Moskal 2007	General population	Alcohol consumption (three categories for dose-response)	colorectal cancer incidence	Yes	prospective cohort studies	01-Jun-05	No PubMed only	Yes	Partially Only included cohort design	Yes	Yes	Sixteen prospective cohort studies including more than 6,300 patients with colorectal cancer were eligible for inclusion. High alcohol intake was significantly associated with increased risk of colon (RR 5 1.50; 95% CI 5 1.25, 1.79) and rectal cancer (RR 5 1.63; 95% CI 5 1.35, 1.97) when comparing the highest with the	Exclude. Part of WCRF work which was included.

												lowest category of alcohol intake, equivalent to a 15% increase of risk of colon or rectal cancer for an increase of 100 g of alcohol intake per week.	

Endometrial

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Alcohol was not significantly associated with risk of adenocarcinoma of the endometrium (21 studies). RR for light consumption 0.97 (95% CI: 0.92-1.01) and RR for moderate consumption 0.99 (95% CI: 0.84-1.16). Heavy drinking not evaluable.	Exclude. Newer SR that met more criteria included.

Friberg 2010	General population	alcohol consumption	endometrial cancer	Yes	prospective studies	01-Mar-10	Partially Search terms not fully reported	Yes	No	No	Yes	Compared with non-drinkers, women drinking less than 1 drink of alcohol (13 g of ethanol) per day had a lower risk for endometrial cancer; this risk was lower by 4% (95% confidence interval (95% CI): 0.93–1.00) for consumption up to 0.5 drink per day and by 7% (95% CI: 0.85–1.02) for consumption up to 1 drink. However, we found evidence of an increased risk for endometrial cancer for intakes higher than two alcoholic drinks per day: compared with non-drinkers, the risk was higher by 14% (95% CI: 0.95–1.36) for 2–2.5 drinks per day and by 25% (95% CI: 0.98–1.58) for 42.5 drinks per day. Our meta-analysis indicates a possible J-shaped relationship between alcohol intake and endometrial cancer risk.	Exclude. Newer SR that met more criteria included.
Hjartaker 2010	General population	Alcohol consumption	Gynecological cancers	Yes	Cohort and case-control	01-Mar-10	Partially Searched PubMed only	No	No	Yes	No	Endometrial cancers do not seem to be related to alcohol consumption.	Exclude. Methods of analysis insufficient.
Sun 2011	General population	Alcohol consumption	Endometrial cancer	Yes	prospective or case-control	01-Apr-10	Partially Search terms not fully reported and only 180 records retrieved	Yes	No	Yes	No Only examined "ever alcohol use"	Alcohol intake was not significantly associated with the risk of endometrial cancer among prospective studies (relative risk (RR): 1.04;	Exclude. Methods of analysis insufficient.

												95% confidence interval (CI): 0.91-1.18) or among case-control studies (odds ratio (OR): 0.89; 95% CI: 0.76-1.05).	
Turati 2010	General population	Alcohol consumption	Endometrial cancer	Yes	case-control and cohort studies	01-Mar-09	No	Partial	No	No	Yes	Compared to never alcohol drinkers, the odds ratio was 1.03 (95% confidence interval, CI, 0.76–1.41) for B7, 1.27 (95% CI 0.86–1.87) for 8–14, and 1.19 (95% CI 0.80–1.77) for C15 drinks/week, with no trend in risk. Our findings provide evidence that alcohol drinking is not associated with endometrial cancer risk, although a weak positive association for very high drinkers cannot be excluded.	Exclude. Newer SR that met more criteria included.
WCRF 2012	General population	All exposures related to food, nutrition and physical activity	Endometrial cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	31-Dec-12	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes	Ten cohort studies and 12 publications were identified; nine studies were included in the meta-analysis. The summary RR per 10 g/d was 1.01 (95% CI: 0.97-1.06, I2=29.0%, Pheterogeneity =0.18) for all studies combined. There was no indication of publication bias with Egger's test (p=0.24).There was no evidence of a nonlinear association.	Exclude. Newer SR that met more criteria included.
Zhou 2016	General population	Alcohol consumption	Endometrial cancer	Yes	prospective study,	01-Jan-16	Yes	Yes	Yes	Yes	Yes		Include. Met all criteria.

					including cohort and case-control								

Gallbladder

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Heavy drinking was significantly associated with an increased risk of cancer of the gallbladder (RR 2.64 (1.62-4.30); 8 studies) but not light drinking (RR 1.23 (0.84 - 1.83)) or moderate drinking (RR 0.88 (0.68-1.13).	Exclude. Newer SR identified that partially met more of the criteria.
Kan 2011	General population	Alcohol consumption	Extrahepatic bile system cancer (biliary tract including gallbladder, bile ducts and ampulla of Vater)	Yes	Case control or cohort	2010	Yes	Yes	No	Yes	Partial Only analysed by non/low vs. drinkers	The studies provided adjusted overall OR estimates for drinkers versus non-/low drinkers, leading to a pooled adjusted OR of 0.82 (95% confidence interval [CI] = 0.72–0.94, P for heterogeneity = 0.194, I2 = 27.2%). For the heavy drinkers, the adjusted OR significance increased to 1.58 (95% CI = 0.97–2.57, P for heterogeneity = 0.055, I2 = 65.4%), but it had no statistical significance.	Exclude. Newer SR identified that partially met more of the criteria.
WCRF 2015a	General population	All exposures related to food, nutrition and physical activity	Gallbladder cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	31-Mar-13	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes		Include. Met or partially met the most criteria and had adequate methods of analysis.

Ye 2013	General population	Alcohol consumption and smoking	Extrahepatic cholangiocarcinoma	Yes	case-control or cohort	31-May-13	Yes	Yes	Yes	Yes	No Only analysed by non vs. drinkers	Pooled analysis indicated that alcohol drinkers had a similar risk of ECC development as did individuals who did not drink alcohol (summary RR = 1.09; 95%CI: 0.87-1.37). There was moderate heterogeneity among the studies and no evidence of publication bias.	Exclude. Methods of analysis insufficient.

Kidney

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	The RRs were 0.92 (95% CI, 0.86-0.99), 0.79 (95% CI, 0.72-0.86) and 0.80 (95% CI, 0.57-1.14) for light (≤12.5 g/day), moderate (≥50 g/day) and heavy (>50g/day) consumption respectively.	Excluded. Another SR identified that met more of the criteria.
Bellocco 2012	General population	At least three levels of alcohol consumption	Renal cell carcinoma incidence	Yes	case-control or cohort	01-Nov-10	Yes	Yes	Yes	Yes	Yes	The estimated RRs were 0.85 (95% CI: 0.80–0.92) for any alcohol drinking, 0.90 (95% CI: 0.83–0.97) for light drinking (0.01–12.49 g/day), 0.79 (95% CI: 0.71–0.88) for moderate drinking (12.5–49.9 g/day) and 0.89 (95% CI: 0.58–1.39) for heavy drinking (≥50 g/day), respectively. Our meta-analysis supports the hypothesis of a negative effect of moderate alcohol consumption on the risk of renal cell cancer.	Excluded. Another SR identified that met the same amount of criteria but had a more recent.

Cheng 2011	General population	alcohol consumption	renal cell carcinoma incidence	Yes	case-control	01-Mar-10	No	Yes	No	Yes	Yes	An inverse association between alcohol consumption and renal cell carcinoma was observed in both the overall alcohol intake group (OR 0.67, 95% CI 0.62-0.73) and subgroups stratified by sex, study design, geographical region, specific beverages and alcohol assessment. The dose-response meta-analysis showed that an increase in alcohol consumption of 12 g of ethanol per day was associated with a 5% statistically significant decreased risk of renal cell cancer.	Excluded. Another SR identified that met more of the criteria.
Song 2012	General population	Alcohol consumption	Renal cell carcinoma or kidney cancer incidence	Yes	Case-control or cohort	01-Aug-11	Yes	Yes	Yes	Yes	Yes	We observed that alcoholic beverage intake was associated with a lower risk of renal cell cancer in combined analysis of case–control and cohort studies; for total alcoholic beverage intake, combined RRs (95% confidence intervals) comparing top with bottom categories were 0.76 (0.68–0.85) in case–control studies, and 0.71 (0.63–0.78) in cohort studies (P for difference by study design = 0.02)	Excluded. Another SR identified that met the same amount of criteria but had a more recent
WCRF 2015	General population	All exposures related to food, nutrition and physical activity	Kidney cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical	01-Mar-13	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes	The summary RR per 10 g/d was 0.92 (95% CI: 0.86-0.97; I2= 55.1%, Pheterogeneity=0.04) for all studies combined. Egger's test showed evidence of small study bias (p= 0.001). The two smaller studies found stronger inverse associations than the other studies.	Excluded. Another SR identified that met more of the criteria.

					cohort study							Significant heterogeneity was observed and appeared to be explained by the weaker inverse association (compared to other studies) reported by the NIH-AARP study, mainly for men (Lew et al, 2011). The heterogeneity decreased after exclusion of this study (I2 = 25.1%, p=0.263). The highest intake categories were ~11 g of ethanol per day and 2 glasses of more per day respectively. The only study that looked are heavy drinking was the NIH-AARP Diet and Cancer Study (Lew et al, 2011). In this study, the association of alcohol intake and renal cell carcinoma was linear, with no threshold effect among heavy drinkers (30 or more g/d). There is strong evidence that consuming alcoholic drinks decreases the risk of kidney cancer, when consuming up to 30 grams (about 2 drinks) a day. There is insufficient, specific evidence for higher levels of drinking – for example, 50 grams (about 3 drinks) or 70 grams (about 5 drinks) a day.	
Xu 2015	General population	Alcohol drinking	Renal cell carcinoma incidence and kidney cancer mortality	Yes	Cohort studies or nested case-control	01-Feb-15	Yes	Yes	Yes	Yes	Yes		Include. Met all of the criteria.

Liver

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	The RRs were 1.00 (95% CI, 0.85-1.18), 1.08 (95% CI, 0.97-1.20) and 2.07 (95% CI, 1.66-2.58) for light (≤12.5 g/day), moderate (≥50 g/day) and heavy (>50g/day) consumption respectively.	Exclude. WCRF considered quality in report and had a more recent search date.
Chuang 2015	General population	Alcohol consumption	Liver cancer	Yes	Case-control and clinical studies	01-May-14	No Medline only. Limited terms searched	Yes	No	No	Yes	The dose–response relation between alcohol and liver cancer was apparent with RR = 1.08 (95 % CI 1.04–1.11) for 12 g/day (~1 drink), 1.54 (95 % CI 1.36–1.74) for 50 g/day, 2.14 (95 % CI 1.74–2.62) for 75 g/day, 3.21 (95 % CI 2.34–4.40) for 100 g/day, and 5.20 (95 % CI 3.25–8.29) for 125 g/day of alcohol	Excluded. Another SR identified that met more of the criteria.
Heckley 2011	ex-drinkers	Alcohol consumption	Liver cancer	Partially	Cohort and case-control	01-Jun-10	Yes	Yes	Yes	Yes	Yes	The meta-analysis suggests that the risk of liver cancer does indeed fall after cessation by 6-7% a year, but there remains a large uncertainty around this estimate both statistically and in its interpretation	Exclude. PEO only partially met.
Palmer 2012	General population	Any risk factors	Intrahepatic cholangiocarcinoma	Partially subset of liver cancer	Case-control	01-Aug-11	Yes	Partial Insufficient detail	No stated in methodology, but results not reported	Yes	Partial Groups alcoholic liver disease in with alcohol consumption	OR alcohol use: 2.81 (1.52–5.21). Alcohol use is a risk factor for intrahepatic cholangiocarcinoma.	Exclude.

Turati 2014	General population	At least three levels of alcohol consumption	Liver cancer	Yes	Prospective studies (cohort or nested case-control)	01-Apr-13	Yes	Yes	No	Yes	Yes	Compared with non-drinking, the pooled RRs were 0.91 (95% confidence interval, CI, 0.81–1.02) for moderate drinking (<3 drinks per day) and 1.16 (95% CI, 1.01–1.34) for heavy drinking (≥3 drinks per day), with significant heterogeneity among studies. The dose–risk curve suggested a linear relationship with increasing alcohol intake in drinkers, with estimated excess risk of 46% for 50 g of ethanol per day and 66% for 100 g per day.	Excluded. Another SR identified that met more of the criteria. Same group as Bagnardi 2015
WCRF 2015	General population	All exposures related to food, nutrition and physical activity	Liver cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	01-Mar-13	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes		Include.

Lung

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

Bagnardi 2011	Never smokers	Alcohol consumption	Lung cancer	Yes	case-control or cohort	01-Jan-10	No PubMed only	Yes	Partially Explored in sensitivity analysis	Yes	Yes	We selected 10 articles, including 1913 never smoker lung cancer cases. The random-effects pooled relative risk (RR) for drinkers versus nondrinkers was 1.21 [95% confidence interval (CI) 0.95–1.55]. The same figure was 1.05 (95% CI 0.89–1.23) after the exclusion of one outlier study. At the dose–response analysis, RR for an increase in alcohol intake of 10 g/day was 1.01 (95% CI 0.92–1.10).	Exclude. Newer review identified by same author.
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes		Include. Highest quality review with the most recent search dates and reliable methods of analysis.

Chao 2007	General population	Consumption of beer, wine or spirits	Lung cancer	Partial	epidemiological studies	01-Feb-07	No PubMed only	Yes	No	Yes	Yes	The results from this meta-analysis suggest that high consumption of beer and liquors may be associated with increased lung cancer risk, whereas modest wine consumption may be inversely associated with risk.	Exclude. Minimum criteria not met.
Garcia-Lavandeira 2016	Never smokers	Alcohol consumption	Lung cancer	Yes	Meta-analysis, pooled studies, cohort and case-control	01-Mar-16	Yes	Yes	Yes	Yes	No. No meta-analysis, no detail regarding why not undertaken	There is little research available on the effect of alcohol on lung cancer risk for people who have never smoked, and more studies are urgently needed on this topic.	Exclude. Methods of analysis insufficient.

WCRF 2007	General population	All exposures related to food, nutrition and physical activity	Lung cancer	Yes	Case-control, cohort and ecological studies	01-Jul-06	Yes	Partial Pooled discussion, not reported individually	Partial Discussed but not formally assessed	Yes	Yes	The results of the overall dose-response meta-analysis show a RR of 1.024 per 10g per week, but this association was attenuated greatly in analyses limited to studies that adjusted for cigarette smoking, such that there was no overall increase in risk. Because of the importance of smoking as a confounder, the smoking adjusted result is the more important for drawing inferences.	Exclude. Newer review of similar quality Note that update was peer reviewed and discussed by panel in June 2015.

Lymphoma, leukemia, myeloma

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or	All cancers (HL & NHL)	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review	No	Yes	Yes	Hodgkin's lymphoma (RR 0.73 (95% CI 0.59–0.89) for light, RR 0.73 (0.60–0.87) for	Include. Review is newer and while it partially met one criterion, it was considered more

		occasional drinkers						includes 572 studies)				moderate and 0.63 (0.41–0.97) for heavy drinking; 9 studies) and non-Hodgkin's lymphoma (RR 0.88 (0.80–0.97) for light, RR 0.87 (0.81–0.95) for moderate and 0.75 (0.64– 0.88) for heavy drinking; 24 studies) had statistically significant inverse associations with the consumption of alcohol.	comprehensive.
Jin 2014	General population	Alcohol intake	Myelodysplastic syndromes	Yes	Cohort or case-control	NR	No dates NR	Yes	Yes	Yes	Yes	The data indicated a stronger association of alcohol with MDS in individuals who consumed ≥10 g/day (OR=1.55, 95% CI: 1.08-2.21) vs. those who consumed <10 g/day (OR=1.09, 95% CI: 0.78-1.53). This meta-analysis suggests that alcohol intake may increase the risk of MDS in a dose-dependent manner. However, additional well-designed, prospective cohort studies are required to verify these findings and identify other risk factors associated with MDS.	Exclude. Rare cancer outcome. Leukaemia was included.
Psaltopoulou 2015	General population	Alcohol consumption	Multiple myeloma	Yes	Case-control and cohort studies	31-Dec-13	Partially Searched PubMed only	Yes	Yes	Yes	Yes	light drinkers: pooled RR 0.88, (95% CI: 0.76 – 1.02), moderate drinkers: pooled RR 0.87, (95% CI: 0.77– 0.99), heavy drinkers:	Include. More recent and more criteria met, including quality assessment.

												RR 0 .86, (95% CI: 0.53 – 1.38)	
Rota 2014a	General population	Alcohol consumption	Multiple myeloma	Yes	Case-control and cohort studies	31-Aug-13	Yes	Yes	No	Yes	Yes	Compared with non-drinkers, the pooled relative risks were 0.96 (95% CI, 0.81–1.13) for light (i.e. ≤ drink/day) and 0.89 (95% CI, 0.74–1.07) for moderate-to-heavy (i.e. >1 drink/day) alcohol drinkers. The dose–risk analysis revealed a model based MM risk reduction of about 15% at two to four drinks/ day (i.e. 25–50 g of ethanol). The present meta-analysis of published data found no strong association between alcohol drinking and MM risk, although a modest favorable effect emerged for moderate-to-heavy alcohol drinkers	Exclude. Review with newer search date that considered quality was identified.

Rota 2014b	General population	Alcohol consumption	Leukaemia	Yes	Case-control and cohort studies	31-Aug-13	Yes	Yes	No	Yes	Yes	Compared with nondrinkers, the relative risks (RRs) for all leukemia were 0.94 [95% confidence interval (CI), 0.85–1.03], 0.90 (95% CI, 0.80–1.01) and 0.91 (95% CI, 0.81–1.02) for any, light (1 drink/day) and moderate to heavy (>1 drink/day) alcohol drinking, respectively. We did not find an increased risk of leukemia among alcohol drinkers. If any, a modest favorable effect emerged for light alcohol drinking, with a model-based risk reduction of approximately 10% in regular drinkers.	Include. Only SR identified for this outcome.
Tramacere 2012a	General population	Alcohol consumption	Non-Hodgkin's lymphoma	Yes	Case-control and cohort studies	01-Jan-11	Yes	Yes	No	Yes	Yes	Compared with non-drinkers, the pooled RRs were 0.88 for light (≤1 drink per day), 0.87 for moderate (1 to <4 drinks per day), and 0.84 for heavy (≥4 drinks per day) alcohol drinking. This meta-analysis provides quantitative evidence of a favourable role of alcohol drinking on NHL risk, though the lack of a biological explanation suggests caution in the	Exclude. Older and less comprehensive than Bagnardi.

												interpretation of results.	
Tramacere 2012b	General population	Alcohol consumption	Hodgkin's lymphoma	Yes	Case-control and cohort studies	01-Jan-11	Yes	Yes	No	Yes	Yes	Compared with nondrinkers, the pooled relative risks were 0.71 (95% CI, 0.57–0.89) for light (i.e. ≤ drink/day) and 0.73 (95% CI, 0.60–0.87) for moderate-to-heavy (i.e. >1 drink/day) alcohol drinking. This meta-analysis suggests a favourable effect of alcohol on HL, in the absence, however, of a dose–risk relationship. The inverse association was restricted to – or greater in – case–control as compared with cohort studies. This indicates caution in the interpretation of results.	Exclude. Older and less comprehensive than Bagnardi.

Melanoma

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Partial Did not undertaken analysis restricted to studies controlled for sun exposure (or a related measure)	The RRs were 1.11 (95% CI, 0.97-1.27), 1.20 (95% CI, 1.03-1.41) and not evaluable for light (≤12.5 g/day), moderate (≥50 g/day) and heavy (>50g/day) consumption respectively.	Include.
Rota 2014c	General population	Alcohol consumption	Cutaneous melanoma	Yes	Case-control or cohort	30-Apr-12	Partially Searched PubMed only	Yes	No	Yes	Yes	The pooled RR was 1 10 (95% CI 0 96–1 26) for light alcohol drinking (≤ 1 drink per day) and 1 18 (95% CI 1 01–1 40) for moderate-to-heavy drinking. The pooled RR from 10 studies adjusting for sun exposure was 1 15 (95% CI 0 94–1 41), while the RR from six unadjusted studies was 1 27 (95% CI 1 20–1 35).	Exclude. Same group as Bagnardi 2015 and Bagnardi is newer.

Mouth, Pharynx and Larynx

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Ahmad Kiadaliri 2013	Former drinkers	Time since drinking	Laryngeal or pharyngeal cancer	No	Not stated	01-Dec-12							Exclude. PEO not met.
Bagnardi 2013	General population	Light drinkers (≤12.5 g or ≤21 drink) vs. non-drinkers	Oral cavity and pharynx, larynx, esophagus, liver,	Partial	Case-control or cohort	01-Dec-10	Yes	Partial Included table of study characteristics but pooled by	No	Yes	Partial	Low alcohol intake (up to 1 drink/day) was found to significantly	Exclude. PEO only partially met.

			colorectum, breast					cancer site				increase the risk of oral cavity and pharynx cancer (RR = 1.17; 95% CI 1.06–1.29).	
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes		Include. Newest review or updated review and meeting the most criteria.
Druesne-Pecollo 2013	Adults with upper aerodigestive tract cancer	Alcohol consumption	Incidence of second primary cancer	No	Case-control or cohort	01-Jul-12							Exclude. PEO not met.

Islami 2010	General population	At least three levels of alcohol consumption	Incidence of laryngeal cancer	Yes	Case-control or cohort	01-May-10	No Searched PubMed only (but did include extensive search of bibliographies of existing reviews)	Yes	No	Yes	Yes	While light alcohol drinking (<1 drink/day) did not show any significant association with risk of laryngeal cancer (12 studies. RR = 0.88; 95% CI: 0.71–1.08), moderate drinking (>1 to <4 drinks/day) was associated with a 1.5-fold increase in risk (35 studies. RR = 1.47; 95% CI: 1.25–1.72) and heavy drinking (P4 drinks/day) was associated with a 2.5-fold increased risk (33 studies. RR = 2.62; 95% CI: 2.13–3.23). Subgroup analyses for studies that adjusted for main potential confounding factors (age, sex, and tobacco use) and several further subgroup analyses showed similar results, which suggest the robustness of the results.	Exclude. Same group as Bagnardi 2015 but newer review available.
Jayasekara 2016	General population	Alcohol consumption over time	Incidence of breast, colorectal and upper aerodigestive	Partial	Cohort and case-control	01-Jan-15	Yes	Yes	No	Yes	Yes	Pooled RR was 4.84 (95% CI: 2.51, 9.32) for oral cavity and pharynx, 2.25	Exclude. Only partially meets PEO.

			tract cancer (oral cavity, pharynx, larynx or oesophagus, individually or combined)									(95% CI: 1.49, 3.42) for larynx. Our findings confirm dose-dependent associations between long-term alcohol intake and upper aerodigestive tract cancer.	
Purdue 2008	General population	Epidemiological questionnaire on both alcohol and tobacco consumption	Invasive tumours of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx and HNC unspecified	Partial No systematic review. Meta-analysis from epidemiological consortium.	Case-control (note study is a meta-analysis NOT a systematic review)	NA	No	Partial Confounders not included	No	Yes	Yes	We observed comparable estimates of HNC relative risk for consumption of beer, liquor and, at high consumption levels, wine in our pooled analysis within the INHANCE Consortium. We observed, however, a comparatively weaker risk at low consumption levels for wine than for the other beverage types. Given the presence of heterogeneity in study-specific results and the possible existence of confounding from diet and other lifestyle factors, our findings should be interpreted with caution.	Exclude. Doesn't meet the minimum criteria and only partially meets the PEO.

Tramacere 2010b	General population	At least three levels of alcohol consumption	Incidence of oral and pharyngeal cancers	Yes	Case-control or cohort	01-Sep-09	No Searched PubMed only	Yes	No	Yes	Yes	The pooled relative risk (RR) was 1.21 (95% confidence interval, CI, 1.10–1.33) for ≤1 drink per day, and rose to 5.24 (95% CI, 4.36–6.30) for heavy alcohol drinking (≥ drinks per day). The dose-risk analysis resulted in RR of 1.29 for 10 g ethanol/day, 3.24 for 50 g ethanol/day, 8.61 for 100 g ethanol/day, and 13.02 for 125 g ethanol/day. This meta-analysis provides more precise evidence of a gross excess of oropharyngeal cancer risk for heavy alcohol drinkers. It also indicates an increased risk for moderate doses, i.e., ≤1 drink or 10 g ethanol/day.	Exclude. Same group as Bagnardi 2015 but newer review available.
Turati 2013	General population (assumed)	Heavy drinking (<= 4 drinks/day), moderate (1-2 drinks/day), drinking in general, and non or occasional drinking	Oral and pharyngeal cancer	Yes	Case-control and cohort studies	1-Sep-10	No - PubMed only	Yes	No	No	Authors used a random-effects model for the meta-analysis and meta-regression. Study stratified by sex, study design, geography, smoking habit	"The association between alcohol and oral and pharyngeal cancer was similar in men and women, with similar dose-response relationships. Among never/non-current	Exclude superseded by Bagnardi 2015

												smokers, the pooled RRs were 1.32 (95% CI 1.05 to 1.67) for drinking and 2.54 (95 CI 1.80 to 3.58) for heavy drinking; for heavy smokers, the RR was 2.92 (95% CI 2.31 to 3.70) for drinking and RR was 6.32 (95% CI 5.05 to 7.90) for heavy drinkers"	
WCRF 2007	General population	Exposures relating to Food, nutrition, physical activity	Mouth, pharynx and larynx	Yes	Case-control, cohort and ecological studies	01-Jun-04	Yes	Yes	Partial Discussed but not formally assessed	Yes	Yes	Five cohort studies, 89 case-control studies, and 4 ecological studies investigated alcoholic drinks and mouth, pharynx, and larynx cancers. All five cohort studies showed increased risk for the highest intake group when compared to the lowest , which was statistically significant in four. Meta-analysis was possible on two studies, giving a summary effect estimate of 1.24 (95% confidence interval (CI) 1.18–1.30) per drink/week, with no heterogeneity. All cohort studies adjusted for smoking. Meta-	Exclude. Outside the search dates of the overview. The updated report is due in 2017.

												analysis was possible on 25 case-control studies, giving a summary effect estimate of 1.03 (95% CI 1.02–1.04) per drink/week, with high heterogeneity. Heterogeneity related to the size, and not the direction, of effect, and is largely explained by varying design and quality of studies. A continuous curvilinear dose-response relationship was apparent from cohort and case-control data with no obvious threshold. There was some evidence of publication bias as a result of small studies that did not report a significant association being unpublished. However, such small studies may suffer from issues of quality. The evidence that alcoholic drinks are a cause of mouth, pharynx, and larynx cancers is convincing. Alcohol and tobacco	

												together increase the risk of these cancers more than either acting independently. No threshold was identified.	
Zhang 2015b	General population	At least three levels of alcohol and tobacco consumption	Oral cavity, pharynx and larynx	Yes	Case-control or cohort	01-Mar-14	Yes	Partial Did not included confounders	No	Yes	No Collected data for alcohol and tobacco but no consideration of their interaction	In patients with alcohol consumption, the pooled odds ratio (OR) and 95% confidence interval (CI) were 1.29(1.06-1.57), 2.67(2.05-3.48) and 6.63(5.02-8.74) for light drinkers, moderate drinkers and heavy drinkers, respectively.	Exclude. Methods of analysis insufficient.

Oesophageal

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Jayasekara 2016	General population	Alcohol consumption over time	Incidence of upper aerodigestive tract cancer (oral cavity, pharynx, larynx or oesophagus, individually or combined)	Partial	Cohort and case-control	01-Jan-15	Yes	Yes	No	Yes	Yes	The pooled RR was 6.71 (95% CI: 4.21, 10.70) for oesophageal cancer. Our findings confirm dose-dependent associations between long-term alcohol intake and oesophageal cancer.	Exclude. Only partially meets PEO and quality not considered.

WCRF 2016c	General population	All exposures related to food, nutrition and physical activity	oesophageal squamous cell carcinomas and oesophageal adenocarcinomas	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	01-Feb-14	Partial Searched PubMed only (justified)	Yes	Partial Study quality considered in report	Yes	Yes		Include. Met/partially met the most criteria and study quality considered in the review.
Liu 2014	General population	Any type of dietary pattern	Oesophageal squamous cell carcinoma	Partial	Cohort, case-control or RCT	01-Dec-13	Yes	Yes	Yes	Yes	No no dose response or multi-category meta-analysis	Drinker/alcohol pattern was related to a significantly increased risk (OR = 2.34, 95% CI: 1.22, 3.45)	Exclude. Insufficient methods of analysis.
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	For oesophagus (squamous cell carcinoma (SCC); RR 1.26 (1.06–1.50) for light (≤12.5 g/day), RR 2.23 (1.87–2.65) for moderate(≤50 g/day) and 4.95 (3.86–6.34) for heavy (>50g/day) drinking; 54 studies) respectively.	Exclude. More recent review that considered study quality included.
Bagnardi 2013	General population	Light drinkers (≤12.5 g or ≤21 drink) vs. non-drinkers	Oral cavity and pharynx, larynx, esophagus, liver, colorectum, breast	Partial	Case-control or cohort	01-Dec-10	Yes	Partial Included table of study characteristics but pooled by cancer site	No	Yes	Partial	Light drinking (up to 1 drink/day) was associated with the risk of esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09–1.56)	Exclude. Partial meets PEO and methods of analysis.

Tramacere 2012c	General population	Alcohol consumption	Esophageal and gastric cardia adenocarcinoma	Yes	case control or cohort	01-Oct-10	Partially Searched PubMed only	Yes	No	Yes	Yes	Compared with nondrinkers, the pooled RRs were 0.86 (95% CI 0.75–0.99) for light (<1 drink per day), 0.90 (95% CI 0.73–1.10) for moderate (1 to <4 drinks per day), and 1.16 (95% CI 0.92–1.46) for heavy (‡4 drinks per day) alcohol drinking. The dose–risk model found a minimum at 25 g/day, and the curve was <1 up to 70 g/day. This meta-analysis provides definite evidence of an absence of association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption.	Exclude. Same group as Bagnardi 2015 Note that this paper is on oesophageal adenocarcinoma, not squamous cell carcinoma. Results also presented under gastric.

Islami 2011	General population	At least three levels of alcohol consumption	Oesophageal squamous cell carcinoma or all oesophageal carcinomas	Yes	Observational studies	01-Jun-10	No Searched PubMed only	Yes	No	Yes	Yes	In studies adjusted for age, sex, and tobacco smoking, the relative risk (RR) and 95% confidence interval (CI) for the association between light alcohol drinking (12.5 g/d) and risk of ESCC was 1.38 (1.14–1.67). The adjusted RRs (95% CIs) were 2.62 (2.07–3.31) for moderate drinking (>12.5–<50 g/d) and 5.54 (3.92–7.28) for high alcohol intake (50 g/d). In prospective studies, the RR (95% CI) was 1.35 (0.92–1.98) for light, 2.15 (1.55–2.98) for moderate, and 3.35 (2.06–5.46) for high alcohol intakes. Among never-smokers (nine studies), the RR (95% CI) was 0.74 (0.47–1.16) for light, 1.54 (1.09–2.17) for moderate, and 3.09 (1.75–5.46) for high intakes.	Exclude. More recent review that considered study quality included. Same group as Bagnardi 2015

Ovarian

Study	Search date	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

Yan-Hong 2015	01-May-14	General population	Alcohol intake	Ovarian cancer	prospective study (cohort or nested case-control)	Yes	Yes	Yes	Yes	Yes	Yes		Include Mets all criteria.
WCRF 2014	01-Dec-12	General population	All exposures related to food, nutrition and physical activity	Oesophageal squamous cell carcinomas and oesophageal adenocarcinomas	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	Yes	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes	The summary RR per 10 g/day was 1.01 (95% CI: 0.96-1.06; I^2= 7.0%, Pheterogeneity=0.37) for all studies combined (8 studies, 2,954 cases). Egger's test did not show any evidence of publication bias (p= 0.66).	Exclude. Newer review identified that meets more of the criteria.
Bagnardi 2015	01-Sep-12	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Case-control, cohort or nested case-control	Yes	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	RR 0.98 (0.93−1.03, I^2=16%) for light (≤12.5 g/day), RR 1.03 (0.95−1.12, I^2=39%) for moderate(≤50 g/day) and not evaluable for heavy (>50g/day) drinking; 20 studies) respectively.	Exclude. Newer review identified that meets more of the criteria.
Rota 2012b	01-Sep-11	General population	Alcohol intake	Epithelial ovarian cancer	Case-control and cohort	Yes	Partially Searched Medline only, terms brief	Yes	No	Yes	Yes	The RRs were 0.97 (95% CI, 0.92–1.02), 1.03 (95% CI, 0.96–1.11) and 1.09 (95% CI, 0.80–1.50) for light (≤1 drink/day), moderate (>1 to <3 drinks) and heavy drinking (≥3 drinks/day), respectively. This comprehensive meta-analysis provided no evidence of a material association between alcohol drinking and epithelial ovarian cancer risk.	Exclude. Newer review identified that meets more of the criteria.
Hjartaker 2010	01-Mar-10	General population	Alcohol consumption	Gynecological cancers	Cohort and case-control	Yes	Partially Searched PubMed only	No	No	Yes	No	Ovarian cancers do not seem to be related to alcohol consumption	Exclude. Newer review identified that meets more of the criteria.
Kim 2010	01-Dec-08	General population	Wine intake	Epithelial ovarian cancer	Case-control and cohort	Partially	Partially terms brief - only retrieved 19 studies	Yes	No	Yes	Yes	There was no significant difference in epithelial ovarian cancer risk between wine and never drinkers (odds ratio	Exclude. Newer review identified that meets more of the criteria.

												[OR], 1.13; 95% confidence interval [CI], 0.92 to 1.38; random effects)	

Pancreatic

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/ exclude
Alsamarrai 2014	General population	Any modifiable risk or protective factor	acute pancreatitis, chronic pancreatitis and pancreatic cancer (excluding metastatic pancreatic cancer)	Partial Analysis of pancreatic diseases	Prospective cohorts (excluding nested case-control)	31-Dec-12	Partially Not clear that free text terms were used.	Partial Does not state adjustment factors, age, sex	Yes	Yes	No Most data pooled for pancreatic disease. No multicategory analysis for cancer.	The pooled RRs for pancreatic cancer were 1.01 (95% CI, 0.80–1.27; P = .92, I2 = 91%) for alcohol users vs non-users	Exclude. Methods of analysis insufficient.
Bagnardi 2015	General population	At least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	RR 0.95 (0.89−1.01, I^2=40%) for light (≤12.5 g/day), RR 1.03 (0.97−1.09, I^2=25%) for moderate(≤50 g/day) and1.19 (1.11−1.28, I2=0%) for heavy (>50g/day) drinking; 39 studies) respectively.	Exclude. Even though this was the newest review, study quality was considered partially by another review.
Haugvik 2015	General population	Diabetes mellitus, ever smoking, heavy smoking, ever alcohol use, heavy alcohol use, first degree family history of cancer	Gastroenteropancreatic neuroendocrine tumours	Partial uncommon sub-type of pancreatic cancer	Cohort or case-control	26-Oct-13	Yes	Yes	Yes	Yes	Yes	Pooled adjusted OR of 1.09 (95% CI: 0.64–1.85; p = 0.75; I 2 = 85.2%) for ever alcohol use and 2.72 (95% CI: 1.25–5.91; p = 0.01; I 2 = 57.8%) for heavy alcohol use. Alcohol use	Exclude. Newer review identified that is not only a partial match of the PEO.

												may be a risk factor for PNET, but there was considerable heterogeneity in the meta-analysis.	
Lucenteforte 2011	General population	Alcohol consumption	Pancreatic cancer	Partial Not a SR, pooled analysis	Case-control	NA	No	Partial Can't access supplementary tables	No	No	Yes	Compared with abstainers and occasional drinkers (<1 drink per day), we observed no association for light-to-moderate alcohol consumption (≤4 drinks per day) and pancreatic cancer risk; however, associations were above unity for higher consumption levels (OR = 1.6, 95% confidence interval 1.2–2.2 for subjects drinking ≥9 drinks per day).	Exclude. Doesn't meet the minimum criteria.

Tramacere 2010a	General population	At least three levels of alcohol consumption	Pancreatic cancer	Yes	Case-control and cohort	01-Mar-09	Yes	Partial No detail on alcohol categories, collection methods	Yes	Yes	Partial Not explored effects of BMI adjustment	The pooled RR was 0.92 (95% confidence interval, 95% CI, 0.86–0.97) for <3 drinks/day and 1.22 (95% CI, 1.12–1.34) for 3 drinks/day. The increased risk for heavy drinking was similar in women and men, but apparently stronger in cohort studies (RR=1.29), in studies with high quality index (RR=1.30), and did not appear to be explained by residual confounding by either history of pancreatitis or tobacco smoking. This metaanalysis provides strong evidence for the absence of a role of moderate drinking in pancreatic carcinogenesis, coupled to an increased risk for heavy alcohol drinking.	Exclude. Same group as Bagnardi. Newer review included which has more sufficient methods of analysis.
Wang 2016b	General population	Alcohol intake	Pancreatic cancer	Yes	Prospective cohorts	01-Aug-15	Yes	Yes	Yes	Yes	Yes		Include. Newest review that meets all of the criteria.

WCRF 2012	General population	All exposures related to food, nutrition and physical activity	Pancreatic cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	28-Sep-11	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes	Overall, the analyses found no clear linear association between alcohol (as ethanol) (per 10g a day) and pancreatic cancer risk (RR 1.00 (95% CI 0.99- 1.01)) with no heterogeneity observed. A summary estimate from a highest versus lowest comparison did result in a statistically significant increased risk (RR 1.30 (95% CI 1.09-1.54)). There was also evidence of a nonlinear association between alcohol (as ethanol) and pancreatic cancer risk. The risk was significant for those consuming 53.4g ethanol or more a day. Results from two separate pooled analyses on alcohol (as ethanol) and pancreatic cancer risk have been published (See table below) and were included. There is ample evidence, but	Include. Newest review that meets the minimum number of criteria.

												this is inconsistent across the range of intakes. At higher levels of consumption, there is evidence of an increased risk of pancreatic cancer. There is limited evidence of a nonlinear association between alcohol and pancreatic cancer, suggesting an increased risk limited to those consuming more than about 3 drinks a day.	

Prostate

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Prostate cancer (RR 1.04 (1.01–1.08, I2=0%) for light (≤12.5 g/day), RR 1.06 (1.01–1.11, I2=17%) for moderate (≤50 g/day) and 1.09 (0.98–1.21, I2=37%) for heavy drinking (>50g/day); 43 studies).	Exclude. Newer review that meets more of the criteria identified.
Middleton Fillmore 2009	General population	Alcohol consumption	Prostate cancer	Yes	Case-control and cohort	01-Dec-06	Partial Searched PubMed only	Yes	Partial Results analysed using different measures of bias	Yes	Yes	A statistically significant association was found between level of alcohol consumption and prostate cancer. This association warrants further investigation, especially in relation to heavy drinking and the	Exclude. Newer review that meets more of the criteria identified. Same group as Zhao 2016

												documentation of alcohol consumption over many years.	
Rota 2012a	General population	Alcohol consumption	Prostate cancer	Yes	Case-control and cohort	01-Dec-10	Partial Searched PubMed only	Partial Can't access supplementary file	No	No	Yes	The relative risks were 1.05 (95% CI, 1.02–1.08), 1.06 (95% CI, 1.01–1.11), and 1.08 (95% CI, 0.97–1.20) for light (≤1 drink/day), moderate (> 1 to < 4 drinks/day), and heavy alcohol drinking (≥4 drinks/day), respectively. This comprehensive meta-analysis provided no evidence of a material association between alcohol drinking and prostate cancer, even at high doses.	Exclude. Newer review that meets more of the criteria identified. Same group as Bagnardi
WCRF 2014a	General population	All exposures related to food, nutrition and physical activity	Prostate cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	30-Apr-13	Partial Searched PubMed only (justified)	Yes	Partial Study quality considered in report	Yes	Yes	The summary RR for an increase of one alcoholic drink per day was 1.01 (95% CI 0.99-1.02; I2=34.4%; pheterogeneity=0.06; n=25). After stratification by outcome (fatal, advanced, non-advanced) the results remained non-significant.	Exclude. Newer review that meets more of the criteria identified.
Zhao 2016	General population	at least three levels of alcohol consumption	Prostate cancer	Yes	Case-control or cohort studies	01-Dec-14	Yes	Yes	Partially Results analysed using different measures of bias	Yes	Yes		Include. Newest review that meets the most criteria.

Stomach

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bagnardi 2015	General population	At least two levels of alcohol consumption vs	All cancers	Yes	Case-control,	01-Sep-12	Yes	Partial Included table of	No	Yes	Yes	Stomach cancer (RR 0.99	Exclude. Newer

		non-drinkers and/or occasional drinkers			cohort or nested case-control			study characteristics but pooled by cancer site (review includes 572 studies)				(0.92−1.06, I2=55%) for light (≤12.5 g/day), RR 0.97 (0.90−1.04, I2=46%) for moderate (≤50 g/day) and 1.21 (1.07−1.36, I2=41%) for heavy drinking (>50g/day); 39 studies).	review that meets more of the criteria identified.
Fang 2015	General population	Intake of dietary factors	Gastric cancer	Partial	Prospective cohort studies	01-Jun-15	Yes	Partial Confounders not listed	Yes	Yes	No Not clear whether adjusted or unadjusted estimates were used	Dose-response analysis indicated that risk of gastric cancer was increased by 5% per 10 g/day increment of alcohol consumption	Exclude. Met same number of minimum criteria as WCRF 2016a but insufficient methods of analysis.
Tramacere 2012c	General population	Alcohol consumption	Oesophageal and gastric cardia adenocarcinoma	Yes	case control or cohort	01-Oct-10	Partially Searched PubMed only	Yes	No	Yes	Yes	Compared with non-drinkers, the pooled RRs were 0.86 (95% CI 0.75–0.99) for light (<1 drink per day), 0.90 (95% CI 0.73–1.10) for moderate (1 to <4 drinks per day), and 1.16 (95% CI 0.92–1.46) for heavy (‡4 drinks per day) alcohol drinking. The dose–risk model found a minimum at 25 g/day, and the curve was <1 up to 70 g/day. This meta-analysis provides definite evidence of an absence of association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption.	Exclude. Newer review that meets more of the criteria identified. Same group as Bagnardi 2015 (note results also presented under oesophageal)

Tramacere 2012d	General population	Alcohol consumption	Gastric cancer	Yes	Case control or cohort	01-Jun-10	Partially Searched PubMed only	Yes	No	Yes	Yes	Compared with nondrinkers, the pooled relative risk (RR) was 1.07 [95% confidence interval (CI) 1.01–1.13] for alcohol drinkers and 1.20 (95% CI 1.01–1.44) for heavy alcohol drinkers (‡4 drinks per day). The pooled estimates were apparently higher for gastric noncardiac (RR for heavy drinkers = 1.17, 95% CI 0.78–1.75) than for gastric cardia (RR = 0.99, 95% CI 0.67–1.47) adenocarcinoma. The dose–risk model estimated a RR of 0.95 (95% CI 0.91–0.99) for 10 g/day and 1.14 (95% CI 1.08–1.21) for 50 g/day.	Exclude. Newer review that meets more of the criteria identified. Same group as Bagnardi 2015
WCRF, 2016a	General population	All exposures related to food, nutrition and physical activity	Gastric/stomach cancer	Yes	Randomised controlled trial, group randomised controlled trial, prospective cohort, nested case-control study, case-cohort study or historical cohort study	01-Feb-14	Partially Searched PubMed only (justified)	Yes	Partially Study quality considered in report	Yes	Yes		Include. Newest review that met the most criteria.

Thyroid

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

									systematic review?				
Wang 2016a	General population	Alcohol consumption	Thyroid cancer	Yes	Cohort or case-control	Aug-15	Partial	Partial	Yes	Yes	Yes		Include. Most recent search date that met the most number of criteria.
Bagnardi 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers	Yes	Case-control, cohort or nested case-control	01-Sep-12	Yes	Partial Included table of study characteristics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes	Thyroid cancer (RR 0.81 (0.74−0.88, I2=0%) for light (≤12.5 g/day), RR 0.81 (0.71−0.94, I2=37%) for moderate (≤50 g/day) and not evaluable for heavy drinking (>50g/day); 9 studies).	Exclude. Newer review that meets more of the criteria identified.
Tsekouras 2013	Adult population	Alcohol consumption or smoking	Thyroid cancer	Yes	Case control	31-Dec-09	Yes	Partial Likely in supplementary material (can't access)	Yes	Yes	Partial Only analysed for ever drinker vs never drinker	For alcohol drinking, mean association was inverse (OR: 0.795; 95% CI: 0.660–0.958) (remaining after adjustment for smoking, OR: 0.832; 95% CI: 0.688–1.007); heterogeneity was large becoming moderate after adjustment.	Exclude. Not Can't access supplementary material
Dal Maso 2009	Adult population	Nutritional factors	Thyroid cancer	Yes	Case control and prospective studies	Jul-07	Partial PubMed only	Partial	No	No	Partial	No effect on TC risk of alcohol emerged	Exclude. Only partially meets PEO and does not meet the minimum criteria

Other cancers

Study	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude

									review?				
Leoncini 2015	General population	Any risk factor	Neuroendocrine tumours	Yes	Cohort and case-control	Jun-14	Yes	Yes	Yes	Yes	No Does not include >3 levels of exposure	Alcohol consumption (pancreas and rectum; OR of 2.44 [95% CI 1.07-5.59, I(2) = 65.8%, P = 0.054] and of 1.53 [95% CI 0.99-2.35, I(2) = 0.0%, P = 0.630] for heavy drinkers versus never-drinkers at meta-analysis for pancreas and rectum).	Exclude. Insufficient methods of analysis.
Leonardi-Bee 2012	Adult population	Smoking, alcohol or BMI	Non-melanoma skin cancer, cutaneous squamous cell carcinoma or basal cell carcinoma	Yes	Comparative observational epidemiological studies	Oct-10	Yes	Partial	Yes	Yes	No Does not include >3 levels of exposure	Alcohol was not significantly related to increased risks of non-melanoma skin cancer (1 study), basal cell carcinoma (Odds Ratio 1.03, 95% CI 0.94 to 1.13, I2=0%, 9 studies) or cutaneous squamous cell carcinoma (1 study). Limited evidence has been published about the risk of non-melanoma skin cancer with alcohol.	Exclude. Insufficient methods of analysis.
Chen 2008	General population	Alcohol intake	Nasopharyngeal	Yes	Case-control	Apr-06	Yes	Yes	Yes	Yes	Yes		Excluded - search

													date 2006

Osteoporosis

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Berg 2008	Yes	General population	Alcohol consumption compared to non-drinkers	Osteoporosis	Experimental (none included) Cohort Case-control	Yes	14-May-07	Yes	Yes	Yes	Yes	Yes	Compared with abstainers and heavier drinkers, persons who consume 0.5 to 1.0 drinks per day have a lower risk of hip fracture. Although available evidence suggests a favorable effect of alcohol consumption on bone density, a precise range of beneficial alcohol consumption cannot be determined.	Include
Drake 2012	Yes	Men	Risk factors - including alcohol but reference group is unclear.	Low BMD related fractures	RCT Observational	No	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	N/A (unclear comparator and study types searched for)	Exclude. Does not meet PEO/study type criteria.
Huiting 2014	Yes	Adults with serious mental illness	Risk factors	Osteoporosis Fractures from osteoporosis	RCT (none identified) Observational	Partial	2012	Yes	Partial - confounders not stated	Yes	Yes	No - insufficient detail about alcohol studies.	Participants with schizophrenia with alcohol dependence also had lower bone mineral density (0.73 g/cm2) than those without (0.78 g/cm2), t (223)= 1.95, p<0.05). Inconsistent evidence existed to suggest the	Exclude. Insufficient detail about alcohol studies.

													impact of gender and alcohol consumption on the prevalence of osteoporosis in people with schizophrenia.	
Papaioannou 2009	Yes	Men 50+ years	Risk factors	Low BMD and bone loss	Cohort Cross-sectional Case-control	Partial	Jan-06	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Only partially meets PEO/study type criteria.
Waugh 2009	Yes	Women 40-60 years	Risk factors	Low BMD and bone loss	Cohort Cross-sectional Case-control	Partial	Jan-06	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Only partially meets PEO/study type criteria.

Gout

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Singh 2011	Yes	General population	Partial - Any risk or prevention factors, including alcohol	Gout	Not defined in methods	Partial	Jun-10	PARTIAL - Medline only searched - Reference lists not stated were searched - MESH terms/search strategy stated in Appendix 1	PARTIAL Confounders adjusted for not stated Sex and age stated	No	No	No	Alcohol consumption increased the risk of incident gout, especially beer and hard liquor.	Exclude. Does not meet minimum criteria.
Wang 2013	Yes	General population	Alcohol where non/occasional drinking is the reference group	Gout	Cohort Case-control	Yes	Jan-13	PARTIAL - PubMed, Web of Science, Google Scholar and Wanfang Med Online searched - Reference lists searched - MESH terms/search strategy not stated	Yes	No	Yes	Yes	The results suggested that alcohol consumption might be associated with increased risk of gout.	Include

Respiratory diseases

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Lonnroth 2008	Yes	General population	Amount of alcohol intake or alcohol use disorder	Tuberculosis	Cohort Case-control	Yes	Not stated	Partial - one database searched and private WHO collection, search dates not stated.	Partial - no age or sex reported	No	Yes	Yes	The risk of active tuberculosis is substantially elevated in people who drink more than 40 g alcohol per day (RR 3.50 (95% CI: 2.01–5.93)), and/or have an alcohol use disorder.	Include
Rehm 2009	Yes	General population	Amount of alcohol intake or alcohol use disorder	Tuberculosis	Systematic reviews	No. Systematic reviews included. Lonnroth 2008 included.	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Incorrect study type included.
Samokhavalov 2010a	Yes	General population	Three or more categories of alcohol consumption.	Pneumonia	Cohort Case-control (specifically excluded cross-sectional)	Yes	Aug-09	Yes	Partial - no age reported	No	Yes	Yes	Alcohol was found to be a risk factor for pneumonia. Individuals consuming 24, 60, and 120 g of pure alcohol daily demonstrated RRs for incident CAP of 1.12 (95% CI 1.02–1.23), 1.33 (95% CI 1.06–1.67) and 1.76 (95% CI 1.13–2.77), respectively, relative to non-drinkers. Clinically defined alcohol-use disorders were associated with an eightfold increased risk of CAP (RR 8.22, 95% CI 4.85–	Include

													13.95).	

Seizures (as a co-morbidity)

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Samokhvalov 2010c	Yes	General population	Three or more categories of alcohol consumption.	Unprovoked seizures Epilepsy morbidity	Cohort Case-control	Yes	Sep-08	Yes	Partial - no age or sex reported	No	Yes	Yes	Author's conclusion: A strong and consistent association between alcohol consumption and epilepsy/unprovoked seizures was found with an overall RR of 2.19 [95% CI 1.83–2.63]. There was a dose–response relationship between the amount of alcohol consumed daily and the probability of the onset of epilepsy. Individuals consuming an average of four, six, and eight drinks daily had RRs of 1.81 (95% CI 1.59–2.07), 2.44 (95% CI 2.00–2.97), and 3.27 (95% CI 2.52–4.26), respectively, compared to nondrinkers.	Include
Walsh 2016	Yes	General population	Alcohol consumption	Epilepsy	No. Only includes systematic review on alcohol by Samokhvalov 2010, identified in the overview.	No. Incorrect study type included.	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Excluded. Incorrect study type included. Includes systematic review on alcohol by Samokhvalov 2010, which is included in the overview.

Cognitive impairment/dementia

Study	Systematic review?	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude?
Anstey 2009	Yes	General population	Alcohol consumption	Dementia and cognitive decline	Yes	Prospective cohort	Jun-07	Yes	Confounders not stated.	No	Yes	Yes	The meta-analysis comparing light to moderate drinking (ranges included 1-21, 1-27, 2-28, 1-14 or unspecified units per week) was a protective factor compared to non-drinking. For Alzheimer's disease a pooled RR 0.72 (95% CI 0.61-0.87). For Vascular dementia a pooled RR 0.75 (95% CI 0.57-0.98). For any dementia a pooled RR 0.74 (95% CI 0.61-0.91). The meta-analysis comparing heavy drinking to not drinking was not significant. The meta-analysis comparing drinking to not drinking reported drinkers had reduced risk of AD (RR=0.66, 95% CI 0.47–0.94) and any dementia (RR=0.66, 95% CI 0.53–0.82)	Include. Most recent systematic review that meets the minimum criteria.

													but was not significant for cognitive decline.	
Beydoun 2014	Yes	General population	Modifiable factors	Cognitive function, decline and dementia	No	No - includes cross-sectional	Oct-12	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)
Cao 2016	Yes	General population	Dietary patterns	Dementia	No	Cohort Systematic review	Sep-14	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)
Daviglus 2011	Yes	50+ years in developed countries	Risk factors	Dementia	No	RCT Cohort Systematic review	27-Oct-09	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)
Di Marco 2014	Yes	General population	Modifiable lifestyle patterns	Dementia	Partial - includes alcohol as a potential risk factor but is not the sole exposure focus of the SR.	Longitudinal cohort	Dec-13	Partial - reference lists not searched	no	no	yes	No analysis or justification of why.	Most studies included in this review suggest that mild-to-moderate alcohol consumption could have a protective role against dementia.	Exclude. Does not meet minimum criteria.
Etgen 2011	No	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)	N/A (not a systematic review)
Lafortone 2016	Yes	all adults aged 40-64 and <40 in populations at higher risk of health inequalities	Behavioural risk factors (including alcohol consumption)	Dementia Disability Frailty QoL (not for alcohol) Cardiovascular diseases and stroke Renal disease Cancer COPD Type II diabetes Osteoporosis and bone health Mental health	Partial - includes alcohol as a potential risk factor but is not the sole exposure focus of the SR.	Protocol specifies longitudinal cohort (the studies included also appear to be case-control) Specifically excluded cross-sectional	Dec-14	No - search was very broad due to number of outcomes but limited MeSH terms for a manageable number of hits. Time constraints meant no had searches carried out.	Yes	Yes	Yes	Narrative synthesis (reports: due to the methodological and statistical heterogeneity it was not appropriate to conduct a meta-analysis.)	There is consistent evidence demonstrating an association between alcohol abstinence and/or heavy drinking and cognitive impairment [52,164–166]. Compared to moderate alcohol intake, alcohol abstinence was associated with a higher risk of poor executive function and poor memory [52]. One study reported no	Exclude. Search terms very broad and not comprehensive.

													association with impairment cognition or dementia	
Lee 2010	Yes	People aged 65 years and older	Paper did not group any of the studies with wide variation across studies. Categories ranged from frequent (>once/month) to wine 1 to 2 times week vs < once a week	Cognitive decline, cognitive impairment and all types of dementia	Yes	Cohort studies	Aug-08	PubMed, Embase and PsycINFO	No - there were no specifics on the population apart from age. Two confounders under consideration were nebulous and the implications unclear (e.g. health-related variables)	Yes - a points-based scoring system: level A (excellent, scored 16 points or above), level B (good, scored 12 to 15 points) or Level C (limited, scored fewer than 12 points)	Yes	Authors decided to provide a table of results with a narrative summary rather than conduct a meta-analysis	There was no meta-analysis. This is because of heterogeneity in measurement and categorisation of health behaviour, cognitive outcome assessment and study population characteristics. "Moderate alcohol consumption tended to be protective against cognitive decline and dementia, but nondrinkers and frequent drinkers exhibited a higher risk for dementia and cognitive impairment"	Exclude superseded by Anstey 2009
Neafsey 2011	Yes	General population	Moderate alcohol consumption	Cognitive risk (outcome insufficiently defined)	No	Any	2011	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)	N/A (incorrect study types and outcome included)
Patterson 2007	Yes	General population	modifiable risk factors (alcohol is moderate wine consumption only)	Dementia	No	Longitudinal cohort	Dec-05	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)
Peters 2008	Yes	General population	Alcohol consumption compared to none	Dementia and cognitive decline	Yes	Cohort Case-control Nested case-control	Mar-06	Yes	No - can't obtain supplementary	No. States studies were assessed for quality but does not say how and does not state quality rating of studies.	Yes	No - the study meta-analysed only drinking (any level), compared to non-drinking and did not do any separate analysis of levels of analysis.	Meta-analyses reported alcohol consumption may be protective against dementia (RR 0.63; 95% CI 0.53–0.75) and Alzheimer's disease (RR	Exclude. Does not meet minimum criteria.

													0.57; 0.44–0.74) but not for vascular dementia (RR 0.82; 0.50–1.35) or cognitive decline (RR 0.89; 0.67–1.17).	
Piazza-Gardner 2013	Yes	General population	Alcohol consumption	Alzheimer's disease	No	Cohort Case-control Meta-analysis Cross-sectional	Not stated	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)
Stavro 2013	Yes	Alcoholics defined by DSM (III, III-TR, IV, IV-TR) or ICD-10 criteria	Alcohol use but no comparator group	Cognition	No. Incorrect exposure	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)	N/A (incorrect exposure)

Diabetes and insulin resistance

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude?
Balianus 2009	Yes	General population	Alcohol consumption compared to current and lifetime abstainers	Diabetes	Cohort Case-control	Yes	31-Jan-08	Yes	Yes	No	No	Yes	Our analysis confirms previous research findings that moderate alcohol consumption is protective for type 2 diabetes in men and women.	Exclude. Systematic review with a more recent search date and that meets more of the protocol criteria identified.
Huang 2016	Yes	General population	Specific alcohol beverages including wine, beer, spirits.	Diabetes	Prospective cohort	No	Feb-16	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	NA (incorrect exposure)	Compared with beer or spirits, wine was associated with a more significant decreased risk	Exclude. Incorrect exposure.

													of type 2 diabetes. The present study showed that wine might be more helpful for protection against type 2 diabetes than beer or spirits.	
Knott 2015	Yes	Adults aged 16 and over	Three or more categories of alcohol consumption, including never or non-drinking.	Diabetes	Cohort Case-control Case-cohort Nested case-control	Yes	18-Feb-14	Medline, EMBASE, CINAHL, ETOH. Reference lists searched Free-text keywords and combinations stated.	Yes	Yes Newcastle-Ottawa scale	Yes	Yes. Fractional polynomial regression	Reductions in risk among moderate alcohol drinkers may be confined to women and non-Asian populations. Although based on a minority of studies, there is also the possibility that reductions in risk may have been overestimated by studies using a referent group contaminated by less healthy former drinkers.	Include. Newest review that meets all criteria.
Li 2016	Yes	General population	Alcohol consumption compared to abstainers	Diabetes	Prospective cohort	Yes	24-Mar-15	Yes	Yes	Yes. NOS	Yes	No. Did not investigate heterogeneity sufficiently. Results for men and women are reported in the text, which it is unclear from the graphs how this result was determined.	Light and moderate alcohol consumption was associated with a lower risk of T2D, whereas heavy alcohol consumption was not related to the risk of T2D.	Exclude, due to methods of analysis.

Mental health disorders

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Boden 2011	Yes	Alcohol misusers only	Only one category of alcohol use: Alcohol misuse	Partial - Depression in those with alcohol misuse. Also looked at Depression>alcohol misuse and comorbid prevalence only.	Longitudinal Cross-sectional	No. Incorrect comparator and study type included.	Not stated	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	Exclude. Doesn't meet PEO/study type criteria.
Conner 2009	Yes	Alcohol misusers only	Only one category of alcohol use: Alcohol misuse	Partial - Depression in those with alcohol misuse. Also looked at Depression>alcohol misuse and comorbid prevalence only.	Not stated	No. Incorrect comparator and study type included.	Sep-07	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	Exclude. Doesn't meet PEO/study type criteria.
Debell 2014	Yes	Alcohol misusers only	Only one category of alcohol use: Alcohol misuse	Partial - PTSD in those with alcohol misuse. Also looked at PTSD>alcohol misuse and comorbid prevalence only.	No - Includes secondary analysis of RCTs. Includes cohort, cross-sectional, case-control, secondary analysis of RCTs.	No. Incorrect comparator and study type included.	9-Aug-12	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	N/A (doesn't meet PEO/study type criteria)	Exclude. Doesn't meet PEO/study type criteria.

Central neurological disorders

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Bettiol 2015	Yes	People with Parkinson's disease and a comparator/control group of people without PD	Quantity and frequency of alcohol or alcoholism	Parkinson's disease	Not defined in methods Cohort Case-control Nested case-control	Yes	May-14	PubMed, TRIP and Web of Science Reference lists searched Search terms stated but MESH terms not stated	Yes	No	Yes	No - no meta-analysis and no justification as to why.	Sixteen articles were identified. No overall conclusions were made as the studies were not synthesised.	Exclude. Methods of analysis insufficient.
Meng 2016	Yes	General population	Alcohol consumption	medically diagnosed ALS	Cohort Case-control	Yes	Nov-15	PARTIAL - PubMed, Web of Knowledge,	No. Levels of alcohol are not stated for all the included	Yes Newcastle-Ottawa scale	Yes	No. Levels are not analysed, just drinker versus non-	The systematic review concludes that compared to	Exclude. Methods of analysis insufficient.

								Elsevier and Science Direct searched - Reference lists searched - Search terms not comprehensive and MESH terms/search strategy not stated	studies. Confounders adjusted for stated Sex, age and other baseline characteristics not stated.			drinker and the levels of alcohol are not stated for all the included studies. Note: text states overall OR = 0.57, 95%CI 0.51-0.64) but the forest plot states OR = 0.64 (0.49-0.83)	not drinking, alcohol consumption reduces the risk of ALS. The systematic review reported OR = 0.54 95% CI 0.45-0.63 for the cohort study and OR=0.60, 95% CI 0.51-0.72).	
Noyce 2012	Yes	Population-based screening	Any risk or prevention factors, including alcohol	Parkinson's disease	Cohort Case-control	Partial	Mar-11	N/A (Alcohol as an individual exposure was not extractable)	N/A (Alcohol as an individual outcome was not extractable)	N/A (Alcohol as an individual outcome was not extractable)	N/A (Alcohol as an individual outcome was not extractable)	N/A (Alcohol as an individual outcome was not extractable)	N/A (Alcohol as an individual outcome was not extractable)	Exclude. Alcohol as an individual outcome was not extractable
Zhang 2014b	Yes	General population	Alcohol consumption	Parkinson's disease	Matched case-control Unmatched case-control Prospective cohort	Yes	Oct-13	PARTIAL - PubMed and Embase searched - Reference lists searched - Search terms not comprehensive and MESH terms/search strategy not stated	PARTIAL Confounders adjusted for stated. Sex, age and other baseline characteristics not stated.	Yes Newcastle-Ottawa scale	Yes	No. levels are not analysed, just drinker versus non-drinker and the levels of alcohol are not stated for all the included studies.	Alcohol intake, especially beer, might be inversely associated with risk of Parkinson's disease.	Exclude. Methods of analysis insufficient.
Zhu 2015	Yes	General population	Alcohol consumption	Multiple sclerosis	Cohort Case-control	Yes	Jun-14	PARTIAL - PubMed, Web of Science and Embase searched - Reference lists searched - Search terms not comprehensive and MESH terms/search strategy not stated	PARTIAL Confounders adjusted and age range for stated. Sex and other baseline characteristics not stated.	Yes Newcastle-Ottawa scale	Yes	No The levels of alcohol in the studies were not extracted and the information of what level of alcohol or comparators that determine the OR/RR cannot be determined.	There may be a potential protective effect of alcohol consumption on MS incidence. The odds ratios (OR) of the association between alcohol consumption and multiple sclerosis were 0.92 [95 % CI 0.73–1.17] overall, 0.91 (95 % CI 0.39–2.41) for prospective study, and 0.92	Exclude. Methods of analysis insufficient.

													(95 % CI 0.72–1.19) for retrospective studies.	

Fertility

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Homan 2007	Yes	General population and the infertile populations undergoing ART	Lifestyle factors including alcohol	Fertility	Cohort Case-control	Partial	2005	Medline, PubMed, CINAHL. Reference lists not searched Specific free-text keywords and combinations not stated.	No.	No. States studies were assessed for quality but does not say how and does not state quality rating of studies.	No	No analysis or justification why and inadequate reporting of results from studies. Only key papers for each lifestyle factor were reported and no explanation of how they were chosen is given.	No conclusion overall for alcohol given. Studies not synthesised and only key papers were reported and no explanation of how they were chosen is given.	Exclude. Doesn't meet minimum criteria.
Ricci 2016	Yes	Men	Alcohol consumption	Semen quality	Cross-sectional	No	Apr-16	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	N/A (incorrect study type included)	Exclude. Incorrect study type included.

Obesity/overweight

Study	Systematic review?	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/Exclude
Bendsen 2013	Yes	General population	Beer only	Obesity	Observational Experimental	No.	Nov-10	N/A. Incorrect study types included	N/A. Incorrect study types included	N/A. Incorrect study types included	N/A. Incorrect study types included		The available data provide inadequate scientific evidence to assess	Exclude. Only on one type of alcohol examined.

													whether beer intake at moderate levels (<500 mL/day) is associated with general or abdominal obesity. Higher intake, however, may be positively associated with abdominal obesity.	
Sayon-Orea 2011	Yes	General population	Alcohol intake	Body weight	Prospective cohort Cross-sectional Intervention (reported separately)	Partial	Mar-10	Partial. Only searched one database.	Yes.	Yes.	No.	No. No meta-analysis conducted and no justification. Also included studies that compared alcohol to no alcohol and not varying levels.	The overall results do not conclusively confirm a positive association between alcohol consumption and weight gain; however, positive findings between alcohol intake and weight gain have been reported, mainly from studies with data on higher levels of drinking. It is, therefore, possible that heavy drinkers may experience such an effect more commonly than light drinkers. Moreover, light-to-moderate alcohol intake, especially wine intake, may be more likely to protect against weight gain,	Exclude. Insufficient methods of analysis.

													whereas consumption of spirits has been positively associated with weight gain.	

Question 3

Study	Systematic review?	Population	Exposure	Outcome	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: comprehensive literature search?	Criteria 2: characteristics of included studies in systematic review?	Criteria 3: quality assessment of included studies in systematic review?	Criteria 4: inclusion/exclusion criteria?	Methods of analysis	Author's conclusion	Include/exclude
Bay 2011	Yes	Pregnant women	Daily, moderate and binge drinking	Child motor function	Yes	Case–control cohort	Feb-2010	Yes	Yes	Partial - nos but not reported for individual studies	Yes	Yes	While it appears consistent that high daily alcohol intake is associated with deficits in gross and fine motor function, and low weekly intake is not associated with such deficits, the issue of binge drinking is unsettled.	Include
Bell 2014	Yes	Pregnant women	Alcohol consumption, binge level drinking, and heavy and moderate levels of consumption vs. No or low levels of consumption	Orofacial clefts in infants	Yes	Case–control cohort	Jul-2013	Partial reference lists not searched	No - levels of alcohol, age and confounders not stated	Yes - NOS	Yes	Only alcohol v no alcohol and binge drinking v no alcohol but no levels of alcohol consumption	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Caputo 2016	Yes	Pregnant women	Fetal alcohol exposure	FASD	No	NR	2016	Yes	No	No	No	No	N/A doesn't meet the PEO/minimu	Exclude. Doesn't meet PEO.

													m criteria	
Flak 2014	Yes	Pregnant women	Mild, moderate and binge prenatal alcohol consumption	Child neuropsychological - different scales - not defined sufficiently	No - insufficient details on exposure and inappropriate analysis.	Case–control cohort	Aug-2012	Yes	No. Confounders not reported	Yes - NOS	Yes	No - meta-analysis combines all studies with widely varied alcohol exposures and all ages combined	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Gronimus 2009	Yes	Pregnant women	Prenatal alcohol exposure - doses not defined	ADHD	Partial	Case–control cohort cross-sectional	2008	Yes	Yes	No	Poorly reported	Meta-analysis of 3 studies	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Latimer 2012	Yes	Pregnant women	Prenatal alcohol consumption	Behavioural disorders	Yes	Case-control Cohort	April 2009	Yes	No. Confounders not reported	No	Yes	No. No meta-analysis and does not justify why.	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Leng 2016	Yes	Pregnant women	Periconceptional alcohol consumption	Neural tube defects	No – incorrect timing of exposure.	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO
Lucas 2016	Yes	Children diagnosed FASD or moderate or heavy maternal alcohol intake	Diagnosed FASD or PAE	Gross motor deficits	No	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A doesn't meet the PEO	Exclude. Doesn't meet PEO.
Liu 2016	Yes	Animals	Prenatal alcohol consumption	Liver dysfunction	No – not in humans	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO	N/A doesn't meet the PEO
Molma-Solana 2013	Yes	Pregnant women	Environmental factors	Cleft lip and palate	Partial	Case–control Cross-sectional	NA methods of analysis insufficient	NA methods of analysis insufficient	NA methods of analysis insufficient	NA methods of analysis insufficient	NA methods of analysis insufficient	No. Alcohol v no alcohol, all levels combined.	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of

														alcohol.
O'Keefe 2014	Yes	Pregnant women	Prenatal alcohol consumption	Communication delay Communication development	Yes	Case–control cohort	March 2012	Yes	Yes	Yes	Yes	Yes. No meta-analysis but justified.		Include.
O'Leary 2010	No. Overview of systematic reviews, meta-analysis and articles.	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review	NA not a systematic review
Polanska 2015	Yes	Pregnant women	Prenatal smoking and alcohol	Neurodevelopment	Yes	Case–control cohort	NR	Yes	Yes	No	Yes	No. No meta-analysis and does not justify why.		Exclude. Methods of analysis insufficient to provide reliable interpretation of results
Sun 2015	Yes	Pregnant women	Alcohol consumption before and during pregnancy	Congenital heart defects	No - insufficient details on exposure.	Case–control cohort	16-feb-2015	Yes	No - drinkers vs non-drinkers only	Yes	Yes	No - meta-analysis combines all studies	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Tripathee 2016	Yes	Pregnant women	Maternal alcohol consumption insufficient details of levels	Microtia	No - insufficient details on exposure.	Case–control	2014	Yes	No	No	Yes	No	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Tsang 2016	Yes	Children diagnosed FASD	Diagnosed FASD	Behavioural problems	No	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A (wrong population)	N/A doesn't meet the PEO	Exclude. Doesn't meet PEO.
Viteri 2015	No	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	N/A not a systematic review	Exclude. Not a systematic review.
Wen 2016	Yes	Pregnant women	Maternal alcohol consumption	Congenital heart defects	No - insufficient details on exposure.	Case–control cohort	Dec-2014	Yes	No -alcohol dose not reported	No	Yes	No - meta-analysis combines all studies	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by

														levels of alcohol.
Yang 2015	Yes	Pregnant women	Prenatal alcohol consumption	Congenital heart defects	No - insufficient details on exposure.	Case–control cohort	Mar-2015	Yes	No -alcohol dose not reported	Yes	Yes	No - meta-analysis combines all studies	N/A doesn't meet the PEO/minimum criteria	Exclude. Methods of analysis insufficient to provide reliable interpretation of results by levels of alcohol.
Zhang 2015	Yes	Pregnant women	Maternal alcohol consumption but no levels of alcohol were analysed or reported from the included studies.	Cryptorchidism	No - insufficient details on exposure.	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	N/A (insufficient details on exposure)	Exclude. Insufficient details on exposure.
Zwink 2011	Yes	Pregnant women	Maternal alcohol consumption – including any alcohol consumption	Anorectal malformations	Yes	No. All levels of alcohol consumption analysed together.	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	N/A (incorrect study types included)	Exclude. All levels of alcohol consumption analysed together.

Mendelian randomisation

Study	Systematic Review	Population	Exposure & comparators	Outcome(s)	Meets PEO/study type criteria?	Study type	Search date	Criteria 1: comprehensive literature search	Criteria 2: clearly specified characteristics of included studies?	Criteria 3: risk of bias assessment completed for included studies	Criteria 4: specified inclusion and exclusion criteria?	Criteria 5: explicitly stated methods ?	Other comments	If meets inclusion criteria, authors' conclusions	Include or exclude?
Bocca 2009	Yes	Japan	ALDH polymorphisms	Head and neck cancer	Unclear	6 case-control studies	31-Jan-08	Yes, Medline and EMBASE	Probably yes	No	Yes	Unclear		"The overall OR from the meta-analysis was 0.53 (95% CI 0.28 to 1.00) for the risk of head and neck cancer among *2*2 homozygotes compared with *1*1 homozygotes and 1.83 (95% CI 1.21 to 2.77) relative to *1*2."	Possibly include, although no stratification by alcohol consumption
Brunner 2017	International consortium (UICC)	Europe, UK, USA, Australia	Database of Alcohol-metabolising genetic variants (ADHs or ALDHs) in the USA, Australia and European countries only	Prostate cancer incidence	Unclear	25 studies, unspecified	NA	NA	Unclear	No	No	Unclear	Examined study specific associations of 68 single nucleotide polymorphisms (SNPs) in 8-alcohol metabolising genes (ADHs and ALDHs)	"No SNPs exceed the Nyhold threshold for association with a diagnosis of prostate cancer"	Possibly include
Chang 2012	Yes	Asia, Europe, North America, Latin America	ADH1B or ADH1C polymorphisms	Head and neck cancer	Unclear	ADH1B: 12 hospital-based and 1 population-based studies; ADH1C: 17 hospital-based and 4 population-based studies; presumably case-control studies	11-Mar-11	No, PubMed only	Unclear	No	Yes	Unclear	Analyses stratified by "high" (includes heavy drinkers) and "low" consumption groups	ADH1B: "Carrying a 2 allele was associated with a reduced risk of head and neck cancer (meta OR 0.50, 95% CI 0.37 to 0.69)" . ADH1C: "Carriers of the 1 allele had a reduced risk of head and neck cancer (OR 0.87, 95% CI 0.76 to 0.99)"	Possibly include

Chikritzhs 2015	Commentary on Holmes 2014	NA	NA	NA	NA	Commentary	NA	NA	NA	NA	NA	NA		NA	Exclude
Fang 2015	Yes	Japan, China, Australia, Europe, UK	ADH1C *1*2 polymorphism (Ile350Val, rs698)	Pancreatitis	Unclear	9 case-control studies	3-Jun-14	Yes, PubMed, Web of Science, OVID	Unclear	No	Yes	Unclear	Stratified analysis conducted only for ethnicity	"An association between ADH1C *1/*2 polymorphism and pancreatitis risk (OR 1.53, 95% CI 1.12 to 2.10 for 1*2 vs *2*2, OR 1.44 95% CI 1.07 to 1.95 for *1*1 + *1*2 vs *2*2)"	Possibly include, although no stratification by alcohol consumption
Guo 2012	Yes	China, Japan, Iran, India, Thailand	ADH1B (His47Arg, rs1229984)	Upper aerodigestive tract cancer (UATC)	Unclear	18 case-control studies	1-Jul-10	No, PubMed only	Unclear	No	Yes	Unclear	Additional analysis based on non-drinking people and drinkers (included low, moderate and heavy drinkers)	"When Arg carriers and homozygote Arg/Arg were compared with homozygous His/His genotype, statistical significance was found between case and control groups, the ORs were 1.66 (95% CI 1.54 to 1.79, p< 0.001 for fixed-effect model) and 3.47 (95% CI 2.76 to 4.36 P < 0.001 for random-effects model)"	Possibly include

He 2015	Yes	China, Europe, UK, Australia, Korea, India, Russia, Japan, and 'Mixed"	ADH2 polymorphism	Liver cirrhosis	Unclear	21 case-control studies	10-Jan-15	Yes, PubMed, Web of Science, CNKI, Wanfang and VIP databases	Unclear	No	Yes	Unclear	Stratified analysis conducted only for ethnicity	"Overall, the ADH2 polymorphism was associated with a decreased risk of ALC in all genetic models (dominant model: OR 0.56 (95% CI 0.38 to 0.83); recessive model: OR 0.59 (95% CI 0.39 to 0.91); *1*2 vs *1*1: OR 0.58, 95% CI 0.40 to 0.85; *2*2 vs *1*1 OR 0.35, 95% CI 0.16 to 0.75)"	Possibly include, although no stratification by alcohol consumption
Holmes 2014	Individual participant data from 56 studies	Multiple countries	Carriers of the A-allele of ADH1B variant vs non-carriers	Coronary heart disease; stroke	Unclear	Unspecified	N/A, a consortium of trialists	NA	Unclear	No	No	Unclear	IPD also looked at the likelihood of alcohol consumption in carriers vs non carriers	"A-allele ADH1B carriers showed reduced odds of coronary heart disease (OR 0.90, 95% CI 0.84 to 0.96, I2=17%). Further division of the drinkers into light (> 0 to <7 units/week), moderate (>7 to <21 units/week) and heavy (>21 units/week) showed the same protective effect of the variant across all alcohol categories". "No association of ADH1B A -allele was identified with the combined subtypes of stroke, although carriers of A-allele had lower odds of ischaemic stroke (OR 0.85, 0.72 to 0.95)"	Probably include. This is a gold-standard IPD however it does not conform to the pre-specified PEO or minimum quality inclusion criteria

Hongguang 2013	Yes	China, Korea, Japan, USA, Russia, Denmark	ADH or ALDH genetic polymorphisms	Coronary artery disease; myocardial infarction	Unclear	12 case - control studies	1-Dec-12	Yes; PubMed, EMBASE, Web of Science, Chinese Biomedicine databases	Unclear	Yes, STROBE	Yes	Unclear		"Mutant genotypes of the rs671 polymorphism in the ALDH2 gene were associated with increased risk of both CAD (RR 1.20, 95% CI 1.03 to 1.40; P = 0.021) and MI (RR 1.32, 95% CI 1.11 to 1.57, P = 0.002). However there were no significant associations of ADH genetic polymorphisms to CAD and MI risk (CAD RR 0.92, 95%CI 0.73 to 1.15, P = 0.445; MI RR 0.93, 95% CI 0.84 to 1.03, P = 0.148)"	Possibly include
La Vecchia 2008	No	North America, Europe, Japan and Europe	ALDH polymorphisms	Laryngeal cancer	NA	Non-systematic literature review	NA	No, PubMed only	NA	NA	NA	NA	Narrative description of studies	NA	Exclude
Li 2011	Yes	European, Asian, African and Mexican ancestries	ADH1B gene (rs1229984 or ARG48His)	Alcohol dependence, some studies had no explicit description of alcohol dependence)	Unclear	73 case-control studies	Unspecified	Unclear - English- and Chinese-language publications	Unclear	No	No	Unclear		"Results suggested strong associations with alcohol dependence and abuse as well as alcohol-induced liver diseases with an allelic (Arg vs His) p value being 1 x10 (-36) and OR 2.06 (95% CI 1.84 to 2.31) using random-effects model"	Possibly exclude

Li 2012	Yes	European, Asian, African and Mexican ancestries	ADH1C Ile350Vale (rs698)	Alcohol related liver disease, cirrhosis or chronic pancreatitis	Unclear	53 case-control studies	Aug-10	Yes, PubMed and Chinese Academic Journals	Unclear	No	No	Unclear	Subgroup analysis on subjects diagnosed with heroin and other drug dependence	"Strong association between ADH1C Ile350Val (rs698) and alcohol dependent and abuse"	Possibly include
Mao 2015	Yes	USA	ADH1C (rs698)	Breast cancer	Unclear	4 case-control studies	11-Nov-11	Yes, PubMed, EMBASE, Cochrane Library, VIP and CNKI	Unclear	Yes	Yes	Unclear	Stratified analysis carried out for menopausal status and alcohol consumption (drink or not)	"the ORs for breast cancer risk for ADH1C*1*2 vs ADH1C*2*2 was OR 1.16 (95% CI 0.95 to 1.42), ADH1C*1*1 vs ADH1C*2*2 was OR 1.17 (95% CI 0.95 to 1.44) and ADH1C*1 vs ADH1C*2 was OR 1.05 (95% Ci 0.96 to 1.16)…This meta-analysis suggested that the ADH1C* allele might modestly influence the effect of alcohol on breast cancer but is not an independent risk factor for breast cancer"	Possibly include

Mao 2016	Yes	Asia, Africa and Europe	ADH1B gene Arg47His polymorphism	Oesphageal cancer	Unclear	23 case-control studies	1-Jun-15	Yes, PubMed, Web of Science, Medline, Embase, CNKI and Wangfang	Unclear	No	Yes	Unclear	Subgroup analysis by ethnicity (polymorphism revealed an ethnic difference and geographic variance), alcohol drinking (drinking associated with increased risk of oesphageal cancer OR 3.15, 95% CI 2.66 to 3.74), smoking (Arg/Arg genotype was associated with oesophageal cancer in both non-smokers and smokers) and sex (Arg/Arg genotype of ADH1B Arg47 His variant increased oesphageal cancer risk)	"…the 47His allele was significant associated with the decreased risk of esophageal cancer when compared with the 47 Arg allele in total populations (OR 0.67, 95% CI 0.59 to 0.76, P < 0.00001)"	Possibly include

Wang 2011	Yes	China, Japan	ALDH2 genotype (Glu/Glu & Glu/Lys with Lys/Lys)	Colorectal cancer or colorectal adenoma	Unclear	6 case-control studies	1-May-10	Yes, Medline and EMBASE	Unclear	No	Yes	Unclear	There was considerable heterogeneity with random-effects and fixed-effect models providing different results for the comparison gly/gly vs lys/lys genotype	"Fixed-effect model showed the pooled OR was 1.31 (95% CI 1.01 to 1.70 for Gly/Glu vs Lys/Lys homozygotes" however the random-effects model gave OR 1.25 (95% CI 0.85 to 1.83, P = 0.26). "The overall effect risk for Gly/Lys heterozygotes relative to Lys/Lys homozygotes was 1.13 under a fixed-effect model" and the random-effects model showed a similar result (OR 1.14, 95% CI 0.87 to 1.49)"	Possibly include however there are concerns about the analysis and possible small-study effects
Wang 2012	Yes	USA, Germany, UK, Australia and Denmark	ADH1C genotype	Breast cancer	Unclear	12 case-control studies	28-Feb-11	Yes, PubMed and MEDLINE	Unclear	No	Yes	Unclear	Subgroup analysis were performed by study design (i.e. hospital vs population based) and menopausal status	"…no significant associations were found between ADH1C genotype and breast cancer risk when all studies pooled (ADH1C*1*2 vs ADH1c*2*2: OR 1.07, 95% CI 0.97 to 1.19, ADH1C*1*1 vs ADH1C*2*2 OR 1.16, 95% CI 0.94 to 1.43; dominant model OR1.07 95% CI 0.97 to 1.18; recessive model OR 1.06 95%CI 0.93 to 1.20)"	Possibly include although subgroup analysis only performed on study design and menopausal status

Xue 2012	Yes	African, Asian, European and mixed descendants	ADH1C Ile350 Val polymorphism	Any cancer	Unclear	35 case-control studies	18-Jul-11	Yes, PubMed and EMBASE	Unclear	No	Yes	Unclear	Stratified analysis by cancer types, ethnicity, source of controls and sample size	"There was a wide variation of the 350 Val allele frequency among the controls across different ethnicities…Over all, no significant associations between ADH1C Ile350Val polymorphism and cancer risk were observed in any genetic models"	Possibly include, although no stratification by alcohol consumption
Yang 2010	Yes	Japan, Thailand, China, Africa, Europe	ADH1B and/or ALDH2 polymorphisms	Oesphageal cancer	Unclear	19 case-control studies	1-Apr-09	Yes, Medline, EMBASE and Chinese Biomedical database	Unclear	No	Yes	Unclear	Stratification by alcohol drinking; the authors state "alcohol drinking could be strong confounding variable in comparing genotypes and the risk of esophageal cancer because the genotypes are also related to the amount of alcohol consumption (suppressive in ALDH2*2) and facilitating in ADH1B*1	"The crude OR was 2.91 (95% CI 2.04 to 4.14) for ADH1B*1/*1 (vs ADH1B*2*2) and 1.32 (95% CI 1.17 to 1.49) for ADH1B*1/*2". Also "risk of esophageal cancer is modified by alcohol consumption, ethnicity and gender"	Possibly include

Zhang 2015	Yes	China, Japan, Korea	ALDH2 polymorphisms	Coronary artery disease	Unclear	11 case-control studies	12-Mar-13	Yes, ISI, Medline, PubMed, CNKI, Wanfang and Weipu	Unclear	Yes, scores modified from previous meta-analysis molecular correlational studies	Yes	Unclear	The majority of studies included in Zhang have already been included in Hongguang . Huongguang's review includes additional references	"Variant A allele carriers showed a 48% increased risk of CAD compared with homozygote A allele (OR 1.48, 95% CI 1.18 to 1.87)"	Exclude; superseded by Hongguang 2013
Zhao 2015	Yes	China, Japan, South Africa and Thailand	ALDH2 rs671 G>A polymorphism	Oesphageal cancer	Unclear	31 case-control studies	2013 (no further details)	Yes, PubMed, Embase, MEDLINE and the Chinese Biomedical database	Unclear	No	Yes	Unclear	Stratified analysis was performed to evaluate other environmental factors such as alcohol-drinking status	"Although a protective effect was found in the rs671 homozygote comparison (AA/GG OR 0.69, 95% CI 0.48 to 0.98), the heterozygote comparison was apparently associated with the risk of oesophageal cancer in the Chinese population (AG/GG OR 1.39, 95% CI 1.03 to 1.87)"	Possibly include
Zuo 2014	Uncertain	German, Korean, African American, European American	ADH cluster, and any other significant association from genome-wide associations	Alcohol dependence	Unclear	Mostly case-control genome-wide association studies	NA	No, PubMed only	Unclear	No	No	Unclear		"The variants located within ADH cluster on Chromosome 4 were found to be significantly associated with alcohol dependence at genome-wide level ($p < 5 \times 10^{-8}$) in at least one sample	Exclude, analyses on genome-wide significant associations using human ciseQTLs and RNA expression in rat and mouse brains

List of studies excluded at full-text

Question 1

Injury to self

1. Andreuccetti, G., Carvalho, H. B., Korcha, R., Ye, Y., Bond, J., & Cherpitel, C. J. (2012). A review of emergency room studies on alcohol and injuries conducted in Latin America and the Caribbean region. Drug & Alcohol Review, 31(6), 737-746.
2. Branas, C. C., Han, S., & Wiebe, D. J. (2016). Alcohol Use and Firearm Violence. Epidemiologic Reviews, 38(1), 32-45.
3. Carra, G., Bartoli, F., Crocamo, C., Brady, K. T., & Clerici, M. (2014). Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis. Journal of Affective Disorders, 167, 125-135.
4. Cherpitel, C. J. (2007). Alcohol and injuries: a review of international emergency room studies since 1995. Drug & Alcohol Review, 26(2), 201-214.
5. Chrcanovic, B. R. (2012). Factors influencing the incidence of maxillofacial fractures. Oral & Maxillofacial Surgery, 16(1), 3-17.
6. Kool, B., Ameratunga, S., & Jackson, R. (2009). The role of alcohol in unintentional falls among young and middle-aged adults: a systematic review of epidemiological studies. Injury Prevention, 15(5), 341-347.
7. Hawton, K., Casanas, I. C. C., Haw, C., & Saunders, K. (2013). Risk factors for suicide in individuals with depression: a systematic review. Journal of Affective Disorders, 147(1-3), 17-28.
8. Nunn, J., Erdogan, M., & Green, R. S. (2016). The prevalence of alcohol-related trauma recidivism: A systematic review. Injury, 47(3), 551-558.
9. Taylor, B., Irving, H. M., Kanteres, F., Room, R., Borges, G., Cherpitel, C., . . . Rehm, J. (2010). The more you drink, the harder you fall: a systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. Drug & Alcohol Dependence, 110(1-2), 108-116.

Injury to others

10. Cafferky, B. (2016). Substance use and intimate partner violence: A meta-analysis. Dissertation Abstracts International Section A: Humanities and Social Sciences, 76(11-A(E)), No Pagination Specified.
11. Crane, C. A., Godleski, S. A., Przybyla, S. M., Schlauch, R. C., & Testa, M. (2016). The proximal effects of acute alcohol consumption on male-to-female aggression: A meta-analytic review of the experimental literature. Trauma, Violence, & Abuse, 17(5), 520-531.
12. Devries, K. M., Child, J. C., Bacchus, L. J., Mak, J., Falder, G., Graham, K., . . . Heise, L. (2014). Intimate partner violence victimization and alcohol consumption in women: a systematic review and meta-analysis. Addiction, 109(3), 379-391.
13. Rothman, E. F., McNaughton Reyes, L., Johnson, R. M., & LaValley, M. (2012). Does the alcohol make them do it? Dating violence perpetration and drinking among youth. Epidemiologic Reviews, 34, 103-119.
14. Smith-Marek, E. N., Cafferky, B., Dominguez, M. M., Spencer, C., Van, K., Stith, S. M., & Oliver, M. A. (2016). Military/civilian risk markers for physical intimate partner violence: A meta-analysis. Violence and Victims, 31(5), 787-818.

Harmful drug-alcohol interactions

15. Baldacchino, A., Tolomeo, S., Khan, F., Humphris, G., & Carra, G. (2016). Acute risk factors in fatal opioid overdoses as a result of hypoxia and cardiotoxicity. A systematic review and critical appraisal. Heroin Addiction and Related Clinical Problems, 18(4), 33-42.

STD

16. Baliunas, D., Rehm, J., Irving, H., & Shuper, P. (2010). Alcohol consumption and risk of incident human immunodeficiency virus infection: a meta-analysis. International Journal of Public Health, 55(3), 159-166.
17. Claxton, S. E., DeLuca, H. K., & van Dulmen, M. H. (2015). The association between alcohol use and engagement in casual sexual relationships and experiences: a meta-analytic review of non-experimental studies. Archives of Sexual Behavior, 44(4), 837-856.
18. Scott-Sheldon, L. A., Carey, K. B., Cunningham, K., Johnson, B. T., & Carey, M. P. (2016). Alcohol use predicts sexual decision-making: A systematic review and meta-analysis of the experimental literature. AIDS and Behavior, 20(Suppl 1), 19-39. Rehm, J., Shield, K. D., Joharchi, N., & Shuper, P. A. (2012). Alcohol consumption and the intention to engage in unprotected sex: systematic review and meta-analysis of experimental studies. Addiction, 107(1), 51-59.

Sexual Function

19. Cheng, J. Y., Ng, E. M., Chen, R. Y., & Ko, J. S. (2007). Alcohol consumption and erectile dysfunction: meta-analysis of population-based studies. International Journal of Impotence Research, 19(4), 343-352.

Acute exacerbation of a mental illness

20. Cairns, K. E., Yap, M. B., Pilkington, P. D., & Jorm, A. F. (2014). Risk and protective factors for depression that adolescents can modify: a systematic review and meta-analysis of longitudinal studies. Journal of Affective Disorders, 169, 61-75.

Question 2

All-cause mortality

1. Roerecke, M., Gual, A. and Rehm, J. 2013. Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analyses. Journal of Clinical Psychiatry 74(12) e1181-1189.
2. Roerecke, M. and Rehm, J. 2013. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction 108(9) 1562-1578.
3. Silva Vde, L., Cesse, E.A. and de Albuquerque Mde, F. 2014. Social determinants of death among the elderly: a systematic literature review. Revista Brasileira de Epidemiologia 17 Suppl 2 178-193.
4. Wang, C., Xue, H., Wang, Q. et al. 2014. Effect of drinking on all-cause mortality in women compared with men: a meta-analysis. Journal of Women's Health 23(5) 373-381.

Pancreatic disease

5. Alsamarrai, A., Das, S. L., Windsor, J. A., & Petrov, M. S. (2014). Factors that affect risk for pancreatic disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Clinical Gastroenterology & Hepatology, 12(10), 1635-1644.e1635
6. Irving, H. M., Samokhvalov, A. V., & Rehm, J. (2009). Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. Jop: Journal of the Pancreas [Electronic Resource], 10(4), 387-392.

Central neurological disorders

7. Bettiol, S. S., Rose, T. C., Hughes, C. J., & Smith, L. A. (2015). Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. Journal of Parkinsons Disease Print, 5(3), 425-442.
8. Meng, E., Yu, S., Dou, J., Jin, W., Cai, X., Mao, Y., . . . Yang, R. (2016). Association between alcohol consumption and amyotrophic lateral sclerosis: a meta-analysis of five observational studies. Neurological Sciences, 37(8), 1203-1208.
9. Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Annals of Neurology, 72(6), 893-901.
10. Zhang, D., Jiang, H., & Xie, J. (2014). Alcohol intake and risk of Parkinson's disease: a meta-analysis of observational studies. Movement Disorders, 29(6), 819-822.
11. Zhu, T., Ye, X., Zhang, T., Lin, Z., Shi, W., Wei, X., . . . He, J. (2015). Association between alcohol consumption and multiple sclerosis: a meta-analysis of observational studies. Neurological Sciences, 36(9), 1543-1550.

Gout

12. Singh, J. A., Reddy, S. G., & Kundukulam, J. (2011). Risk factors for gout and prevention: a systematic review of the literature. Current Opinion in Rheumatology, 23(2), 192-202.

Seizures (co-morbidity)

13. Walsh, S., Donnan, J., Fortin, Y., Sikora, L., Morrissey, A., Collins, K., & MacDonald, D. (2016). A systematic review of the risks factors associated with the onset and natural progression of epilepsy. NeuroToxicology., 11.

Obesity

14. Bendsen, N. T., Christensen, R., Bartels, E. M., Kok, F. J., Sierksma, A., Raben, A., & Astrup, A. (2013). Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. Nutrition Reviews, 71(2), 67-87.
15. Sayon-Orea, C., Martinez-Gonzalez, M. A., & Bes-Rastrollo, M. (2011). Alcohol consumption and body weight: a systematic review. Nutrition Reviews, 69(8), 419-431.

Dementia/cognitive impairment

16. Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health, 14, 643.
17. Cao, L., Tan, L., Wang, H. F., Jiang, T., Zhu, X. C., Lu, H., . . . Yu, J. T. (2016). Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies. Molecular Neurobiology, 53(9), 6144-6154.
18. Daviglus, M. L., Plassman, B. L., Pirzada, A., Bell, C. C., Bowen, P. E., Burke, J. R., . . . Williams, J. W., Jr. (2011). Risk factors and preventive interventions for Alzheimer disease: state of the science. Archives of Neurology, 68(9), 1185-1190.
19. Di Marco, L. Y., Marzo, A., Munoz-Ruiz, M., Ikram, M. A., Kivipelto, M., Ruefenacht, D., . . . Frangi, A. F. (2014). Modifiable lifestyle factors in dementia: a systematic review of longitudinal observational cohort studies. Journal of Alzheimer's Disease, 42(1), 119-135.
20. Etgen, T., Sander, D., Bickel, H., & Forstl, H. (2011). Mild cognitive impairment and dementia: the importance of modifiable risk factors. Deutsches Arzteblatt International, 108(44), 743-750.
21. Lafortune, L., Martin, S., Kelly, S., Kuhn, I., Remes, O., Cowan, A., & Brayne, C. (2016). Behavioural Risk Factors in Mid-Life Associated with Successful Ageing, Disability, Dementia and Frailty in Later Life: A Rapid Systematic Review. PLoS ONE [Electronic Resource], 11(2), e0144405.
22. Lee Y, Back JH, Kim J, Kim SH, Na DL, Cheong HK, Hong CH, Kim YG. 2010. Systematic review of health behavioral risks and cognitive health in older adults. *International Psychogeriatrics* 22 (2): 174-187.
23. Patterson, C., Feightner, J., Garcia, A., & MacKnight, C. (2007). General risk factors for dementia: A systematic evidence review. Alzheimer's and Dementia, 3(4), 341-347.
24. Peters, R., Peters, J., Warner, J., Beckett, N., & Bulpitt, C. (2008). Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age & Ageing, 37(5), 505-512.
25. Piazza-Gardner, A. K., Gaffud, T. J., & Barry, A. E. (2013). The impact of alcohol on Alzheimer's disease: a systematic review. Aging & Mental Health, 17(2), 133-146.
26. Neafsey, E. J., & Collins, M. A. (2011). Moderate alcohol consumption and cognitive risk. Neuropsychiatric Disease and Treatment, 7(1), 465-484.
27. Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. Addiction Biology, 18(2), 203-213.

Cardiovascular diseases

1. Bagnardi, V., Zatonski, W., Scotti, L., La Vecchia, C., & Corrao, G. (2008). Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. Journal of Epidemiology & Community Health, 62(7), 615-619.
2. Chen, X., Zhou, L., Zhang, Y., Yi, D., Liu, L., Rao, W., . . . Yi, D. (2014). Risk factors of stroke in Western and Asian countries: a systematic review and meta-analysis of prospective cohort studies. BMC Public Health, 14, 776.
3. Chiva-Blanch, G., Arranz, S., Lamuela-Raventos, R. M., & Estruch, R. (2013). Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies. Alcohol & Alcoholism, 48(3), 270-277.
4. Clarke, M. (2008). Systematic review of reviews of risk factors for intracranial aneurysms. Neuroradiology, 50(8), 653-664.

5. Costanzo S, di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. 2011. Alcohol consumption in relation to vascular and total mortality in patients with diabetes, hypertension or history of cardiovascular disease: a meta-analysis. *Journal of Wine Research* 22(2): 119-122.
6. Djousse, L., & Gaziano, J. M. (2008). Alcohol consumption and heart failure: a systematic review. Current Atherosclerosis Reports, 10(2), 117-120.
7. Huang, C., Zhan, J., Liu, Y. J., Li, D. J., Wang, S. Q., & He, Q. Q. (2014). Association between alcohol consumption and risk of cardiovascular disease and all-cause mortality in patients with hypertension: a meta-analysis of prospective cohort studies. Mayo Clinic Proceedings, 89(9), 1201-1210.
8. Kelso, N. E., Sheps, D. S., & Cook, R. L. (2015). The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review. American Journal of Drug & Alcohol Abuse, 41(6), 479-488.
9. Kodama, S., Saito, K., Tanaka, S. et al. 2011. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *Journal of the American College of Cardiology* 57(4) 427-436.
10. Lippi, G., Mattiuzzi, C., & Franchini, M. (2015). Alcohol consumption and venous thromboembolism: friend or foe? Internal and emergency medicine, 10(8), 907-913.
11. Mente, A., de Koning, L., Shannon, H. S., & Anand, S. S. (2009). A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Archives of Internal Medicine, 169(7), 659-669.
12. Padilla, H., Michael Gaziano, J., & Djousse, L. (2010). Alcohol consumption and risk of heart failure: a meta-analysis. Physician & Sportsmedicine, 38(3), 84-89.
13. Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. BMC Public Health, 10, 258.
14. Roerecke, M., & Rehm, J. (2014). Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers. BMC Medicine, 12, 182.
15. Roerecke, M., & Rehm, J. (2014). Chronic heavy drinking and ischaemic heart disease: A systematic review and meta-analysis. Open Heart, 1 (1) (e000135).
16. Roerecke, M., & Rehm, J. (2010). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. American Journal of Epidemiology, 171(6), 633-644.
17. Roerecke, M., & Rehm, J. (2011). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. American Journal of Epidemiology, 173(3), 245-258.
18. Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction, 107(7), 1246-1260.
19. Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ,
20. Samokhvalov, A. V., Irving, H. M., & Rehm, J. (2010). Alcohol consumption as a risk factor for atrial fibrillation: a systematic review and meta-analysis. European Journal of Cardiovascular Prevention & Rehabilitation, 17(6), 706-712.
21. Wang, C. J., Shen, Y. X., & Liu, Y. (2016). Empirically Derived Dietary Patterns and Hypertension Likelihood: A Meta-Analysis. Kidney and Blood Pressure Research, 41(5), 570-581.
22. Yao, X., Zhang, K., Bian, J., & Chen, G. (2016). Alcohol consumption and risk of subarachnoid hemorrhage: A meta-analysis of 14 observational studies. Biomedical Reports, 5(4), 428-436.
23. Zheng, Y. L., Lian, F., Shi, Q., Zhang, C., Chen, Y. W., Zhou, Y. H., & He, J. (2015). Alcohol intake and associated risk of major cardiovascular outcomes in women compared with men: a systematic review and meta-analysis of prospective observational studies. BMC Public Health, 15, 773.
24. Zhang, X. Y., Shu, L., Si, C. J., Yu, X. L., Liao, D., Gao, W., . . . Zheng, P. F. (2015). Dietary Patterns, Alcohol Consumption and Risk of Coronary Heart Disease in Adults: A Meta-Analysis. Nutrients, 7(8), 6582-6605.
25. Zhang, C., Qin, Y. Y., Chen, Q., Jiang, H., Chen, X. Z., Xu, C. L., . . . Zhou, Y. H. (2014). Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. International Journal of Cardiology, 174(3), 669-677.

Diabetes

26. Baliunas, D. O., Taylor, B. J., Irving, H., Roerecke, M., Patra, J., Mohapatra, S., & Rehm, J. (2009). Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. Diabetes Care, 32(11), 2123-2132.
27. Huang, J., Wang, X., & Zhang, Y. (2016). Specific types of alcoholic beverage consumption and risk of type 2 diabetes: A systematic review and meta-analysis. Journal of Diabetes Investigation.
28. Li, X. H., Yu, F. F., Zhou, Y. H., & He, J. (2016). Association between alcohol consumption and the risk of incident type 2 diabetes: a systematic review and dose-response meta-analysis. American Journal of Clinical Nutrition, 103(3), 818-829.

Liver disease

29. Cao, G., Yi, T., Liu, Q., Wang, M., & Tang, S. (2016). Alcohol consumption and risk of fatty liver disease: A meta-analysis. PeerJ, 2016 (10) (no pagination)(e2633).
30. Roerecke, M., Nanau, R., Rehm, J., & Neuman, M. (2016). Ethnicity matters: A Systematic Review and Meta-Analysis of the Non-Linear Relationship Between Alcohol Consumption and Prevalence and Incidence of Hepatic Steatosis. EBioMedicine, 8, 317-330.
31. Sookoian, S., Castano, G. O., & Pirola, C. J. (2014). Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut, 63(3), 530-532.

Mental disorders

32. Boden, J. M., & Fergusson, D. M. (2011). Alcohol and depression. Addiction, 106(5), 906-914.
33. Conner, K. R., Pinquart, M., & Gamble, S. A. (2009). Meta-analysis of depression and substance use among individuals with alcohol use disorders. Journal of Substance Abuse Treatment, 37(2), 127-137.
34. Debell, F., Fear, N. T., Head, M., Batt-Rawden, S., Greenberg, N., Wessely, S., & Goodwin, L. (2014). A systematic review of the comorbidity between PTSD and alcohol misuse. Social Psychiatry & Psychiatric Epidemiology, 49(9), 1401-1425.

Fertility

35. Homan, G. F., Davies, M., & Norman, R. (2007). The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Human Reproduction Update, 13(3), 209-223.
36. Ricci, E., Al Beitawi, S., Cipriani, S., Candiani, M., Chiaffarino, F., Vigano, P., . . . Parazzini, F. (2016). Semen quality and alcohol intake: A systematic review and meta-analysis. Reproductive BioMedicine Online., 04.

Respiratory diseases

37. Rehm, J., Samokhvalov, A. V., Neuman, M. G., Room, R., Parry, C., Lonnroth, K., . . . Popova, S. (2009). The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health, 9, 450.

Osteoporosis

38. Drake, M. T., Murad, M. H., Mauck, K. F., Lane, M. A., Undavalli, C., Elraiyah, T., . . . Montori, V. M. (2012). Risk factors for low bone mass-related fractures in men: A systematic review and meta-analysis. Journal of Clinical Endocrinology and Metabolism, 97(6), 1861-1870.
39. Huiting, X., Fen, L. Q., Peng, Y., Jia, W., Loh, S., Parasuram, R., & Shan, C. P. (2014). Risk factors for osteoporosis in adults with serious mental illnesses: A comprehensive systematic review. JBI Database of Systematic Reviews and Implementation Reports, 12(6), 60-119.

40. Papaioannou, A., Kennedy, C. C., Cranney, A., Hawker, G., Brown, J. P., Kaiser, S. M., . . . Adachi, J. D. (2009). Risk factors for low BMD in healthy men age 50 years or older: a systematic review. Osteoporosis International, 20(4), 507-518.
41. Waugh, E. J., Lam, M. A., Hawker, G. A., McGowan, J., Papaioannou, A., Cheung, A. M., . . . Perimenopause, B. M. D. G. S. o. O. C. (2009). Risk factors for low bone mass in healthy 40-60 year old women: a systematic review of the literature. Osteoporosis International, 20(1), 1-21.

Cancer

42. Ahmad Kiadaliri, A., Jarl, J., Gavriilidis, G., & Gerdtham, U. G. (2013). Alcohol drinking cessation and the risk of laryngeal and pharyngeal cancers: a systematic review and meta-analysis. PLoS ONE [Electronic Resource], 8(3), e58158.
43. Albuquerque, R. C., Baltar, V. T., & Marchioni, D. M. (2014). Breast cancer and dietary patterns: a systematic review. Nutrition Reviews, 72(1), 1-17.
44. Bagnardi, V., Rota, M., Botteri, E., Scotti, L., Jenab, M., Bellocco, R., . . . Boffetta, P. (2011). Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. Annals of Oncology, 22(12), 2631-2639.
45. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., . . . La Vecchia, C. (2013). Light alcohol drinking and cancer: a meta-analysis. Annals of Oncology, 24(2), 301-308. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., . . . La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. British Journal of Cancer, 112(3), 580-593.
46. Bellocco, R., Pasquali, E., Rota, M., Bagnardi, V., Tramacere, I., Scotti, L., . . . La Vecchia, C. (2012). Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. *Annals of Oncology, 23*(9), 2235-2244.
47. Cheng, G., & Xie, L. (2011). Alcohol intake and risk of renal cell carcinoma: A meta-analysis of published case-control studies. *Archives of Medical Science, 7*(4), 648-657.
48. Bonequi, P., Meneses-Gonzalez, F., Correa, P., Rabkin, C. S., & Camargo, M. C. (2013). Risk factors for gastric cancer in Latin America: a meta-analysis. Cancer Causes & Control, 24(2), 217-231.
49. Cai, S., Li, Y., Ding, Y., Chen, K., & Jin, M. (2014). Alcohol drinking and the risk of colorectal cancer death: a meta-analysis. European Journal of Cancer Prevention, 23(6), 532-539.
50. Chao, C. (2007). Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis. Cancer Epidemiology, Biomarkers & Prevention, 16(11), 2436-2447.
51. Chen, L., Gallicchio, L., Boyd-Lindsley, K., Tao, X. G., Robinson, K. A., Lam, T. K., . . . Alberg, A. J. (2009). Alcohol consumption and the risk of nasopharyngeal carcinoma: a systematic review. Nutrition & Cancer, 61(1), 1-15.
52. Chow, W. H. (2015). Alcohol consumption and survival after a breast cancer diagnosis: A literature-based meta-analysis and collaborative analysis of data for 29,239 cases. Breast Diseases, 25(4), 323-324.
53. Chuang, S. C., Lee, Y. C., Wu, G. J., Straif, K., & Hashibe, M. (2015). Alcohol consumption and liver cancer risk: a meta-analysis. Cancer Causes & Control, 26(9), 1205-1231.
54. Dal Maso, L., Bosetti, C., La Vecchia, C., & Franceschi, S. (2009). Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes & Control, 20(1), 75-86.
55. de Menezes, R. F., Bergmann, A., & Thuler, L. C. (2013). Alcohol consumption and risk of cancer: a systematic literature review. Asian Pacific Journal of Cancer Prevention: Apjcp, 14(9), 4965-4972.
56. Druesne-Pecollo, N., Keita, Y., Touvier, M., Chan, D. S., Norat, T., Hercberg, S., & Latino-Martel, P. (2014). Alcohol drinking and second primary cancer risk in patients with upper aerodigestive tract cancers: a systematic review and meta-analysis of observational studies. Cancer Epidemiology, Biomarkers & Prevention, 23(2), 324-331.

57. Fahey, P. P., Mallitt, K. A., Astell-Burt, T., Stone, G., & Whiteman, D. C. (2015). Impact of pre-diagnosis behavior on risk of death from esophageal cancer: a systematic review and meta-analysis. Cancer Causes & Control, 26(10), 1365-1373.
58. Fang, X., Wei, J., He, X., An, P., Wang, H., Jiang, L., . . . Min, J. (2015). Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. European Journal of Cancer, 51(18), 2820-2832.
59. Fedirko, V., Tramacere, I., Bagnardi, V., Rota, M., Scotti, L., Islami, F., . . . Jenab, M. (2011). Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Annals of Oncology, 22(9), 1958-1972.
60. Feng, Y. L., Shu, L., Zheng, P. F., Zhang, X. Y., Si, C. J., Yu, X. L., . . . Zhang, L. (2016). Dietary patterns and colorectal cancer risk: a meta-analysis. European Journal of Cancer Prevention., 03.
61. Friberg, E., Orsini, N., Mantzoros, C. S., & Wolk, A. (2010). Alcohol intake and endometrial cancer risk: a meta-analysis of prospective studies. British Journal of Cancer, 103(1), 127-131.
62. Galeone, C., Malerba, S., Rota, M., Bagnardi, V., Negri, E., Scotti, L., . . . Pelucchi, C. (2013). A meta-analysis of alcohol consumption and the risk of brain tumours. *Annals of Oncology, 24*(2), 514-523.
63. Galbiatti, A. L., Padovani-Junior, J. A., Maniglia, J. V., Rodrigues, C. D., Pavarino, E. C., & Goloni-Bertollo, E. M. (2013). Head and neck cancer: causes, prevention and treatment. Revista Brasileira de Otorrinolaringologia, 79(2), 239-247.
64. Gao, Y., Huang, Y. B., Liu, X. O., Chen, C., Dai, H. J., Song, F. J., . . . Wang, Y. G. (2013). Tea consumption, alcohol drinking and physical activity associations with breast cancer risk among Chinese females: a systematic review and meta-analysis. Asian Pacific Journal of Cancer Prevention: Apjcp, 14(12), 7543-7550.
65. García-Lavandeira, J. A., Ruano-Ravina, A., & Barros-Dios, J. M. (2016). Alcohol consumption and lung cancer risk in never smokers. Gaceta sanitaria / S.E.S.P.A.S, 30(4), 311-317.
66. Gou, Y. J., Xie, D. X., Yang, K. H., Liu, Y. L., Zhang, J. H., Li, B., & He, X. D. (2013). Alcohol Consumption and Breast Cancer Survival: A Meta- analysis of Cohort Studies. Asian Pacific Journal of Cancer Prevention: Apjcp, 14(8), 4785-4790.
67. Haugvik, S. P., Hedenstrom, P., Korsaeth, E., Valente, R., Hayes, A., Siuka, D., . . . Capurso, G. (2015). Diabetes, smoking, alcohol use, and family history of cancer as risk factors for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Neuroendocrinology, 101(2), 133-142.
68. Heckley, G. A., Jarl, J., Asamoah, B. O., & U, G. G. (2011). How the risk of liver cancer changes after alcohol cessation: a review and meta-analysis of the current literature. BMC Cancer, 11, 446.
69. Hjartaker, A., Meo, M. S., & Weiderpass, E. (2010). Alcohol and gynecological cancers: an overview. European Journal of Cancer Prevention, 19(1), 1-10.
70. Huxley, R. R., Ansary-Moghaddam, A., Clifton, P., Czernichow, S., Parr, C. L., & Woodward, M. (2009). The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. International Journal of Cancer, 125(1), 171-180.
71. Islami, F., Fedirko, V., Tramacere, I., Bagnardi, V., Jenab, M., Scotti, L., . . . La Vecchia, C. (2011). Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: a systematic review and meta-analysis. International Journal of Cancer, 129(10), 2473-2484. Islami, F., Tramacere, I., Rota, M., Bagnardi, V., Fedirko, V., Scotti, L., . . . La Vecchia, C. (2010). Alcohol drinking and laryngeal cancer: overall and dose-risk relation--a systematic review and meta-analysis. Oral Oncology, 46(11), 802-810.
72. Jayasekara, H., MacInnis, R. J., Room, R., & English, D. R. (2016). Long-term alcohol consumption and breast, upper aero-digestive tract and colorectal cancer risk: A systematic review and meta-analysis. Alcohol and Alcoholism, 51(3), 315-330.

73. Jin, M., Cai, S., Guo, J., Zhu, Y., Li, M., Yu, Y., . . . Chen, K. (2013). Alcohol drinking and all cancer mortality: a meta-analysis. Annals of Oncology, 24(3), 807-816.
74. Jin, J., Yu, M., Hu, C., Ye, L., Xie, L., Chen, F., . . . Tong, H. (2014). Alcohol consumption and risk of myelodysplastic syndromes: A meta-analysis of epidemiological studies. *Molecular and Clinical Oncology, 2*(6), 1115-1120.
75. Kan, H. P., Huang, Y. Q., Tan, Y. F., & Zhou, J. (2011). Meta-analysis of alcohol consumption and risk of extrahepatic bile system cancer. Hepatology Research, 41(8), 746-753.
76. Kim, H. S., Kim, J. W., Shouten, L. J., Larsson, S. C., Chung, H. H., Kim, Y. B., . . . Kang, S. B. (2010). Wine drinking and epithelial ovarian cancer risk: A meta-analysis. Journal of Gynecologic Oncology, 21(2), 112-118.
77. Leonardi-Bee, J., Ellison, T., & Bath-Hextall, F. (2012). Lifestyle factors of smoking, BMI and alcohol on the risk of non-melanoma skin cancer in adults: A systematic review. JBI Library of Systematic Reviews, 10(6), 352-398.
78. Leoncini, E., Carioli, G., La Vecchia, C., Boccia, S., & Rindi, G. (2016). Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. *Annals of Oncology, 27*(1), 68-81.
79. Li, Y., Mao, Y., Zhang, Y., Cai, S., Chen, G., Ding, Y., . . . Jin, M. (2014). Alcohol drinking and upper aerodigestive tract cancer mortality: a systematic review and meta-analysis. Oral Oncology, 50(4), 269-275.
80. Liu, X., Wang, X., Lin, S., Yuan, J., & Yu, I. T. (2014). Dietary patterns and oesophageal squamous cell carcinoma: a systematic review and meta-analysis. British Journal of Cancer, 110(11), 2785-2795.
81. Lucenteforte, E., La Vecchia, C., Silverman, D., Petersen, G. M., Bracci, P. M., Ji, B. T., . . . Duell, E. J. (2012). Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Annals of Oncology, 23(2), 374-382.
82. Magalhaes, B., Peleteiro, B., & Lunet, N. (2012). Dietary patterns and colorectal cancer: systematic review and meta-analysis. European Journal of Cancer Prevention, 21(1), 15-23.
83. Mao, Q., Lin, Y., Zheng, X., Qin, J., Yang, K., & Xie, L. (2010). A meta-analysis of alcohol intake and risk of bladder cancer. Cancer Causes & Control, 21(11), 1843-1850.
84. Middleton Fillmore, K., Chikritzhs, T., Stockwell, T., Bostrom, A., & Pascal, R. (2009). Alcohol use and prostate cancer: a meta-analysis. Molecular Nutrition & Food Research, 53(2), 240-255.
85. Moskal, A., Norat, T., Ferrari, P., & Riboli, E. (2007). Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. International Journal of Cancer, 120(3), 664-671.
86. Palmer, W. C., & Patel, T. (2012). Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. Journal of Hepatology, 57(1), 69-76.
87. Pelucchi, C., Galeone, C., Tramacere, I., Bagnardi, V., Negri, E., Islami, F., . . . La Vecchia, C. (2012). Alcohol drinking and bladder cancer risk: a meta-analysis. Annals of Oncology, 23(6), 1586-1593.
88. Pelucchi, C., & La Vecchia, C. (2009). Alcohol, coffee, and bladder cancer risk: a review of epidemiological studies. European Journal of Cancer Prevention, 18(1), 62-68.
89. Prabhu, A., Obi, K. O., & Rubenstein, J. H. (2014). The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. American Journal of Gastroenterology, 109(6), 822-827.
90. Psaltopoulou, T., Sergentanis, T. N., Sergentanis, I. N., Karadimitris, A., Terpos, E., & Dimopoulos, M. A. (2015). Alcohol intake, alcoholic beverage type and multiple myeloma risk: a meta-analysis of 26 observational studies. *Leukemia & Lymphoma, 56*(5), 1484-1501.

91. Purdue, M. P., Hashibe, M., Berthiller, J., La Vecchia, C., Dal Maso, L., Herrero, R., . . . Hayes, R. B. (2009). Type of alcoholic beverage and risk of head and neck cancer--a pooled analysis within the INHANCE Consortium. American Journal of Epidemiology, 169(2), 132-142.
92. Qi, Z. Y., Shao, C., Yang, C., Wang, Z., & Hui, G. Z. (2014). Alcohol consumption and risk of glioma: a meta-analysis of 19 observational studies. *Nutrients, 6*(2), 504-516.
93. Rota, M., Pasquali, E., Bellocco, R., Bagnardi, V., Scotti, L., Islami, F., . . . La Vecchia, C. (2014). Alcohol drinking and cutaneous melanoma risk: a systematic review and dose-risk meta-analysis. British Journal of Dermatology, 170(5), 1021-1028.
94. Rota, M., Pasquali, E., Scotti, L., Pelucchi, C., Tramacere, I., Islami, F., . . . Bagnardi, V. (2012). Alcohol drinking and epithelial ovarian cancer risk. a systematic review and meta-analysis. Gynecologic Oncology, 125(3), 758-763.
95. Rota, M., Porta, L., Pelucchi, C., Negri, E., Bagnardi, V., Bellocco, R., . . . La Vecchia, C. (2014). Alcohol drinking and multiple myeloma risk--a systematic review and meta-analysis of the dose-risk relationship. European Journal of Cancer Prevention, 23(2), 113-121.
96. Rota, M., Porta, L., Pelucchi, C., Negri, E., Bagnardi, V., Bellocco, R., . . . La Vecchia, C. (2014). Alcohol drinking and risk of leukemia-a systematic review and meta-analysis of the dose-risk relation. Cancer Epidemiology, 38(4), 339-345.
97. Rota, M., Scotti, L., Turati, F., Tramacere, I., Islami, F., Bellocco, R., . . . Bagnardi, V. (2012). Alcohol consumption and prostate cancer risk: a meta-analysis of the dose-risk relation. European Journal of Cancer Prevention, 21(4), 350-359.
98. Seitz, H. K., Pelucchi, C., Bagnardi, V., & La Vecchia, C. (2012). Epidemiology and pathophysiology of alcohol and breast cancer: Update 2012. Alcohol & Alcoholism, 47(3), 204-212.
99. Simapivapan, P., Boltong, A., & Hodge, A. (2016). To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review. Cancer Treatment Reviews, 50, 155-167.
100. Singh, J., Ramamoorthi, R., Baxi, S., Jayaraj, R., & Thomas, M. (2014). The risk factors of head and neck cancer and their general patterns in Australia: a descriptive review and update. Journal of Environmental Pathology, Toxicology & Oncology, 33(1), 45-57.
101. Skibola, C. F., Slager, S. L., Berndt, S. I., Lightfoot, T., Sampson, J. N., Morton, L. M., & Weisenburger, D. D. (2014). Medical history, lifestyle, family history, and occupational risk factors for adult acute lymphocytic leukemia: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. Journal of the National Cancer Institute. Monographs, 2014(48), 125-129.
102. Song, D. Y., Song, S., Song, Y., & Lee, J. E. (2012). Alcohol intake and renal cell cancer risk: a meta-analysis. British Journal of Cancer, 106(11), 1881-1890.
103. Sun, Q., Xu, L., Zhou, B., Wang, Y., Jing, Y., & Wang, B. (2011). Alcohol consumption and the risk of endometrial cancer: a meta-analysis. Asia Pacific Journal of Clinical Nutrition, 20(1), 125-133.
104. Tong, G. X., Liang, H., Chai, J., Cheng, J., Feng, R., Chen, P. L., . . . Wang, D. B. (2014). Association of risk of gastric cancer and consumption of tobacco, alcohol and tea in the Chinese population. Asian Pacific Journal of Cancer Prevention: Apjcp, 15(20), 8765-8774.
105. Tramacere, I., Negri, E., Bagnardi, V., Garavello, W., Rota, M., Scotti, L., . . . La Vecchia, C. (2010). A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 1: overall results and dose-risk relation. Oral Oncology, 46(7), 497-503.
106. Tramacere, I., Negri, E., Pelucchi, C., Bagnardi, V., Rota, M., Scotti, L., . . . Boffetta, P. (2012). A meta-analysis on alcohol drinking and gastric cancer risk. Annals of Oncology, 23(1), 28-36.

107. Tramacere, I., Pelucchi, C., Bonifazi, M., Bagnardi, V., Rota, M., Bellocco, R., . . . Negri, E. (2012). A meta-analysis on alcohol drinking and the risk of Hodgkin lymphoma. European Journal of Cancer Prevention, 21(3), 268-273.
108. Tramacere, I., Scotti, L., Jenab, M., Bagnardi, V., Bellocco, R., Rota, M., . . . La Vecchia, C. (2010). Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. International Journal of Cancer, 126(6), 1474-1486.
109. Tramacere, I., Pelucchi, C., Bonifazi, M., Bagnardi, V., Rota, M., Bellocco, R., . . . Negri, E. (2012). Alcohol drinking and non-Hodgkin lymphoma risk: a systematic review and a meta-analysis. *Annals of Oncology, 23*(11), 2791-2798.
110. Tramacere, I., Pelucchi, C., Bagnardi, V., Rota, M., Scotti, L., Islami, F., . . . Negri, E. (2012). A meta-analysis on alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. *Annals of Oncology, 23*(2), 287-297.
111. Tsekouras, V. (2013). Smoking, alcohol and thyroid cancer occurrence: Systematic review and meta-analysis of case-control studies. Expert Review of Endocrinology and Metabolism, 8(6), 505-515.
112. Turati, F., Galeone, C., Rota, M., Pelucchi, C., Negri, E., Bagnardi, V., . . . La Vecchia, C. (2014). Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. Annals of Oncology, 25(8), 1526-1535.
113. Turati, F., Gallus, S., Tavani, A., Tramacere, I., Polesel, J., Talamini, R., . . . La Vecchia, C. (2010). Alcohol and endometrial cancer risk: a case-control study and a meta-analysis. Cancer Causes & Control, 21(8), 1285-1296.
114. Turati F, Garavello W, Tramacere I, Pelucchi C, Galeone C, Bagnardi V, Corrao G, Islami F, Fedirko V, Boffetta P, La Vecchia C, Negri E. 2013. A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses. Alcohol and Alcoholism 48(1): 107-118.
115. Varoni, E. M., Lodi, G., & Iriti, M. (2015). Ethanol versus Phytochemicals in Wine: Oral Cancer Risk in a Light Drinking Perspective. International Journal of Molecular Sciences, 16(8), 17029-17047.
116. Wang, S. S., Flowers, C. R., Kadin, M. E., Chang, E. T., Hughes, A. M., Ansell, S. M., . . . Weisenburger, D. D. (2014). Medical history, lifestyle, family history, and occupational risk factors for peripheral T-cell lymphomas: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. Journal of the National Cancer Institute. Monographs, 2014(48), 66-75.
117. Wang, X., Cheng, W., Li, J., & Zhu, J. (2016). A meta-analysis of alcohol consumption and thyroid cancer risk. Oncotarget, 7(34), 55912-55923.
118. Wang, Y., Duan, H., Yang, H., & Lin, J. (2015). A pooled analysis of alcohol intake and colorectal cancer. International Journal of Clinical and Experimental Medicine, 8(5), 6878-6889.
119. Wang, Y. T., Gou, Y. W., Jin, W. W., Xiao, M., & Fang, H. Y. (2016). Association between alcohol intake and the risk of pancreatic cancer: A dose-response meta-analysis of cohort studies. BMC Cancer, 16 (1) (212).
120. Xu, X., Zhu, Y., Zheng, X., & Xie, L. (2015). Does beer, wine or liquor consumption correlate with the risk of renal cell carcinoma? A dose-response meta-analysis of prospective cohort studies. *Oncotarget, 6*(15), 13347-13358.
121. Yan-Hong, H., Jing, L., Hong, L., Shan-Shan, H., Yan, L., & Ju, L. (2015). Association between alcohol consumption and the risk of ovarian cancer: a meta-analysis of prospective observational studies. BMC
122. Ye, X. H., Huai, J. P., Ding, J., Chen, Y. P., & Sun, X. C. (2013). Smoking, alcohol consumption, and the risk of extrahepatic cholangiocarcinoma: a meta-analysis. World Journal of Gastroenterology, 19(46), 8780-8788.

123. Zeisser C, Stockwell TR, Chikritzhs T. 2014. Methodological biases in estimating the relationship between alcohol consumption and breast cancer: the role of drinker misclassification errors in meta-analytic results. *Alcoholism: Clinical and Experimental Research* 38(8):2297-2306.
124. Zhang, C., & Zhong, M. (2015). Consumption of beer and colorectal cancer incidence: a meta-analysis of observational studies. Cancer Causes & Control, 26(4), 549-560.
125. Zhang, Y., Wang, R., Miao, L., Zhu, L., Jiang, H., & Yuan, H. (2015). Different levels in alcohol and tobacco consumption in head and neck cancer patients from 1957 to 2013. PLoS ONE [Electronic Resource], 10(4), e0124045.
126. Zhao, J., Stockwell, T., Roemer, A., & Chikritzhs, T. (2016). Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer, 16 (1) (no pagination)(845).
127. Zhou, Q., Guo, P., Li, H., & Chen, X. D. (2016). Does alcohol consumption modify the risk of endometrial cancer? A dose-response meta-analysis of prospective studies. Archives of Gynecology and Obstetrics, 1-13.
128. Zhu, J. Z., Wang, Y. M., Zhou, Q. Y., Zhu, K. F., Yu, C. H., & Li, Y. M. (2014). Systematic review with meta-analysis: alcohol consumption and the risk of colorectal adenoma. Alimentary Pharmacology & Therapeutics, 40(4), 325-337
129. Zygogianni, A. G., Kyrgias, G., Karakitsos, P., Psyrri, A., Kouvaris, J., Kelekis, N., & Kouloulias, V. (2011). Oral squamous cell cancer: early detection and the role of alcohol and smoking. Head & neck oncology, 3, 2.

Question 3

1. Bell, J. C., Raynes-Greenow, C., Turner, R. M., Bower, C., Nassar, N., & O'Leary, C. M. (2014). Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. Paediatric and Perinatal Epidemiology, 28(4), 322-332.
2. Caputo, C., Wood, E., & Jabbour, L. (2016). Impact of fetal alcohol exposure on body systems: A systematic review. Birth Defects Research Part C - Embryo Today: Reviews, 108(2), 174-180.
3. Flak, A. L., Su, S., Bertrand, J., Denny, C. H., Kesmodel, U. S., & Cogswell, M. E. (2014). The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. Alcoholism: Clinical & Experimental Research, 38(1), 214-226.
4. Gronimus, R., Ridout, D., Sandberg, S., & Santosh, P. (2009). Maternal alcohol consumption. London Journal of Primary Care(1), 28-35.
5. Latimer, K., Wilson, P., Kemp, J., Thompson, L., Sim, F., Gillberg, C., . . . Minnis, H. (2012). Disruptive behaviour disorders: a systematic review of environmental antenatal and early years risk factors. Child: Care, Health & Development, 38(5), 611-628.
6. Leng, L. Y., Wang, J. W., Cao, S. S., & Wang, M. (2016). Maternal periconceptional alcohol consumption and the risk of neural tube defects in offspring: A meta-analysis. Journal of Maternal-Fetal and Neonatal Medicine, 29(10), 1673-1679.
7. Liu, Q., Gao, F., Liu, X., Li, J., Wang, Y., Han, J., & Wang, X. (2016). Prenatal alcohol exposure and offspring liver dysfunction: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics, 294(2), 225-231.
8. Lucas, B. R., Latimer, J., Pinto, R. Z., Ferreira, M. L., Doney, R., Lau, M., . . . Elliott, E. J. (2014). Gross motor deficits in children prenatally exposed to alcohol: a meta-analysis. Pediatrics, 134(1), e192-209.
9. Molina-Solana, R., Yanez-Vico, R. M., Iglesias-Linares, A., Mendoza-Mendoza, A., & Solano-Reina, E. (2013). Current concepts on the effect of environmental factors on cleft lip and palate. International Journal of Oral & Maxillofacial Surgery, 42(2), 177-184.
10. O'Leary, C. M., & Bower, C. (2012). Guidelines for pregnancy: what's an acceptable risk, and how is the evidence (finally) shaping up? Drug & Alcohol Review, 31(2), 170-183.
11. Polanska, K., Jurewicz, J., & Hanke, W. (2015). Smoking and alcohol drinking during pregnancy as the risk factors for poor child neurodevelopment - A review of epidemiological studies. International Journal of Occupational Medicine & Environmental Health, 28(3), 419-443.
12. Sun, J., Chen, X., Chen, H., Ma, Z., & Zhou, J. (2015). Maternal Alcohol Consumption before and during Pregnancy and the Risks of Congenital Heart Defects in Offspring: A Systematic Review and Meta-analysis. Congenital Heart Disease, 10(5), E216-224.
13. Tripathee, S., Zhang, J., & Xiong, M. (2016). Risk factors of microtia: A systematic review and meta-analysis. European Journal of Plastic Surgery, 39(5), 335-344.
14. Tsang, T. W., Lucas, B. R., Carmichael Olson, H., Pinto, R. Z., & Elliott, E. J. (2016). Prenatal Alcohol Exposure, FASD, and Child Behavior: A Meta-analysis. Pediatrics, 137(3), e20152542.
15. Viteri, O. A., Soto, E. E., Bahado-Singh, R. O., Christensen, C. W., Chauhan, S. P., & Sibai, B. M. (2015). Fetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review. American Journal of Perinatology, 32(5), 405-416.
16. Wen, Z., Yu, D., Zhang, W., Fan, C., Hu, L., Feng, Y., . . . Mo, X. (2016). Association between alcohol consumption during pregnancy and risks of congenital heart defects in offspring: meta-analysis of epidemiological observational studies. Italian Journal of Pediatrics, 42, 12.
17. Yang, J., Qiu, H., Qu, P., Zhang, R., Zeng, L., & Yan, H. (2015). Prenatal Alcohol Exposure and Congenital Heart Defects: A Meta-Analysis. PLoS ONE [Electronic Resource], 10(6), e0130681.

18. Zhang, L., Wang, X. H., Zheng, X. M., Liu, T. Z., Zhang, W. B., Zheng, H., & Chen, M. F. (2015). Maternal gestational smoking, diabetes, alcohol drinking, pre-pregnancy obesity and the risk of cryptorchidism: a systematic review and meta-analysis of observational studies. PLoS ONE [Electronic Resource], 10(3),
19. Zwink, N., Jenetzky, E., & Brenner, H. (2011). Parental risk factors and anorectal malformations: systematic review and meta-analysis. Orphanet Journal Of Rare Diseases, 6, 25.

Appendix 1

Quality assessment instrument

AMSTAR- Quality assessment tool for systematic reviews

The AMSTAR tool is used to assess the quality of systematic reviews. All items are answered with either 'yes', 'no', 'can't answer' or 'not applicable'. An answer of 'yes' is scored as one point and all other answers score zero points.

Table 88 AMSTAR quality assessment instrument

Item	Question	Answer	Comment
1	Was an 'a priori' design provided? [a]		
2	Was there duplicate study selection and data extraction? [b]		
3	Was a comprehensive literature search performed? [c]		
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion? [d]		
5	Was a list of studies (included and excluded) provided? [e]		
6	Were the characteristics of the included studies provided? [f]		
7	Was the scientific quality of the included studies assessed and documented? [g]		
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? [h]		
9	Were the methods used to combine the findings of studies appropriate? [i]		
10	Was the likelihood of publication bias assessed? [j]		
11	Was the conflict of interest stated? [k]		

Abbreviations: CA = can't answer; N = no; NA = not applicable; Y = yes

a. The research question and inclusion criteria should be established before the conduct of the review. Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."
b. There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.
c. 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. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
d. 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. Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.
e. A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."
f. 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. Note: Acceptable if not in table format as long as they are described as above.
g. '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. Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).
h. 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. Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.
i. 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, I2). 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?).Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

j. 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, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
k. Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.

Appendix 2

Data extraction form

Table 89 Data extraction form for systematic reviews

General information	Systematic Review	
	Title	
	Country of origin	
	Source of funding	
	Possible conflicts of interest (for study authors or translators)	
AMSTAR Rating		
Characteristics of review and included primary studies	Aim/objectives of systematic review	
	Search Methods	
	Level of evidence (lowest identified)	
	Study types identified	
	Quality of evidence evaluated and summary of RoB	
	RoB tool used	
	Inclusion criteria	
	Exclusion criteria	
Results: (per outcome)	Definition of outcome	
	Method of measurement	
	No. of studies and participants analysed by type of study	
	No. of studies and participants excluded or missing (with reasons) by type of study	
	Statistical method of analysis	
	Significance/direction	
	Heterogeneity	
	Results	
Authors' conclusion		
Reviewer's notes		

References