



THE UNIVERSITY OF
SYDNEY

Evaluating the evidence on the health effects of alcohol consumption

Evidence evaluation report

NHMRC Clinical Trials Centre
The University of Sydney

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Abbreviations

AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AWC	Alcohol Working Committee
CI	confidence interval
CTC	Clinical Trials Centre
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

Executive summary

Background

An overview of systematic reviews was commissioned by the National Health and Medical Research Council (NHMRC) to assist in providing the evidence base for the update of the 2009 guidance on the health benefits and harms of alcohol consumption. This overview reports and assesses the quality of the evidence about the health effects of varying levels and/or patterns of alcohol consumption.

Objectives

The objectives were to assess:

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

Methods

The research methods protocol of the overview was developed in collaboration with NHMRC. We conducted medical literature searches in multiple clinical and systematic review databases during the period 1 January 2007 to 5 January 2017. References of systematic reviews were screened against the predefined criteria set in the protocol and agreed upon by the Alcohol Working Committee. The exposure and comparator could include varying levels and/or patterns of alcohol consumption (including no alcohol consumption). There were a minimum of 50 predefined outcomes of interest ranging from short-term to long-term effects across the lifespan. We applied a two-stage screening process to select the best available systematic review for each outcome. The best, publically available systematic review was assessed for reporting quality using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist and the underlying evidence quality using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Data were extracted and presented in GRADE tables, and the results were synthesised narratively.

Results

Thirty-eight systematic reviews were included and addressed 3 out of the 4 overview questions. The reporting quality of the included systematic reviews ranged from 2 to 9 (out of 11) on the AMSTAR checklist. Not all included reviews assessed the risk of bias in the primary studies or provided all the key characteristics of the included studies. In those which

did assess the risk of bias, the assessments were often poorly reported and insufficient for reliable interpretation of the review and its included studies.

For the short term health risks and benefits of alcohol consumption associated with any single episode of drinking, 5 outcomes were reported. For the long term health risks and benefits associated with alcohol consumption, 42 outcomes were reported. For the health risks and benefits of alcohol consumption for pregnant women and their fetuses, babies and children, 6 outcomes were reported. No systematic reviews were identified for the health risks and benefits of alcohol consumption for breastfeeding women and their babies. GRADE tables presented under the results section for each health outcome provide more detail.

Quality of evidence in GRADE

The application of GRADE to examining the health effects of exposure to alcohol has limitations, as the evidence is largely observational in nature. Given that randomised controlled trials are not often ethically appropriate or feasible to examine this exposure, observational data studies usually provide the best available evidence. Furthermore, using GRADE to assess the quality of systematic reviews in overviews is a developing methodology and presents further challenges, particularly as the systematic reviews identified in this evidence evaluation often did not contain sufficient information about the included primary studies.

As such the quality of evidence examining the health effects of alcohol consumption across most outcomes was assessed as being very low in GRADE, with some outcomes assessed as having a low or moderate quality rating. In addition to the issues outlined above, this is mainly due to the poor reporting of key aspects of the included studies and also concerns about conduct, including the assessment of the risk of bias of the included primary studies, consideration of confounding factors, exploration of possible causes of heterogeneity, and the risk of publication bias. For further information on methods and limitations refer to the Technical Report.

Introduction

The National Health and Medical Research Council (NHMRC) is responsible for developing and issuing guidelines and health advice to the Australian community. In March 2009, NHMRC released the Australian Guidelines to Reduce Health Risks from Drinking Alcohol⁸³ (the 2009 Alcohol Guidelines).

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 the NHMRC recommended to NHMRC's Chief Executive Officer that the 2009 Alcohol Guidelines be updated.

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

Background

Alcohol is a central nervous system depressant that inhibits brain functions, dampens the motor and sensory centres, and makes judgment, coordination and balance more difficult¹. The consumption of alcohol is widespread in Australia where regular alcohol use is acceptable to the majority of Australians and part of many social and cultural activities^{4, 29}. However, more than 20% of adults drink in excess of current guideline recommendations²⁰.

Alcohol-related harms are generally associated with patterns of drinking, and involve a complex interplay between a person's age, general health, and genetic and social environment^{30, 83}. The harmful use of alcohol is the third highest contributor to the global burden of diseases, leading to premature deaths and disabilities¹⁶³. The World Health Organization (WHO) estimated that 3.3 million people worldwide died of alcohol-related causes in 2012 and alcohol was responsible for 139 million disability-adjusted life years (DALYs), or 5.1% of the global burden of disease and injury¹⁶⁴.

In Australia, the prevalence of alcohol use disorders (including alcohol dependence and harmful use of alcohol) was estimated at 3.5% (5.0% in males; 2.1% in females) in 2010, and the prevalence of heavy drinking was 10.9% (16.8% in males; 5.1% in females)¹⁶⁴.

The misuse of alcohol is one of the leading causes of preventable death in Australia²⁹. Alcohol has been causally linked to more than 60 medical conditions, with estimates suggesting that it causes 3,430 deaths per year²⁰.

According to the 2009 Alcohol Guidelines, healthy adults who drink on average no more than 2 standard* drinks per day have a lower lifetime risk of harm from alcohol-related disease or injury, compared to those drinking more than 2 standard drinks per day. The guidelines also state that those drinking no more than four standard drinks on a single occasion, compared to those drinking more than 4 standard drinks on a single occasion, have a reduced risk of alcohol-related injury arising from that occasion⁸³.

*An Australian standard drink contains 10 g of alcohol (equivalent to 12.5 mL of pure alcohol)

Consumption trends in Australia

There has been an overall decrease in alcohol consumption in Australia in the past decade. Daily and weekly alcohol use have declined, and a significantly higher proportion of people drink less often than weekly (2 to 3 days a month, once a month, or less often than once a month)⁴.

The proportion of people drinking in excess of the 2009 recommendation declined from 21% in 2004 to 18.2% in 2013, and to 17.1% in 2016; while the percentage of single occasion risky drinkers has remained relatively stable over the years⁴. Figure 1 illustrates the overall percentage of abstainers, single occasion drinkers and lifetime risky drinkers in the Australian population from 2001 to 2016. Lifetime risky drinkers have been defined as people who consume more than two standard drinks per day (on average over a 12 month period), and single occasion risky drinkers as people consuming 5 or more standard drinks on a single occasion⁴.

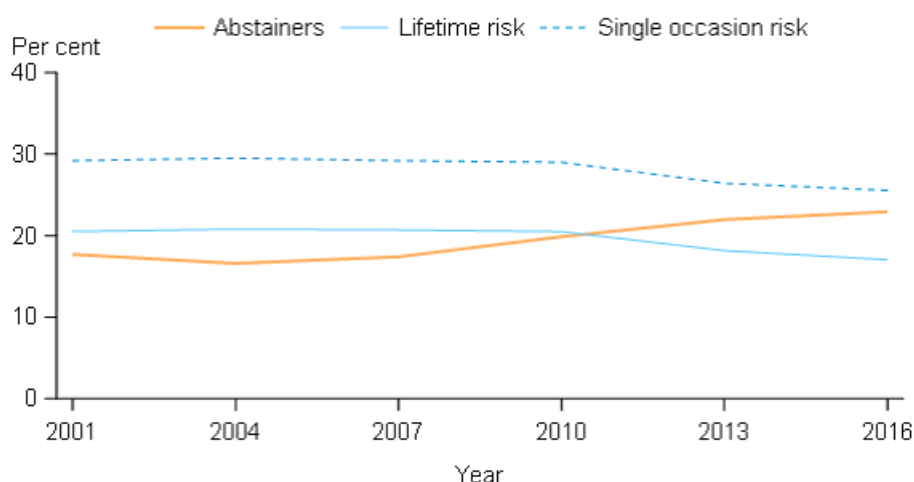


Figure 1 Percentage of people aged 14 years or older by risk levels or abstaining, 2001 to 2016
Source: AIHW 2017⁴

In the past decade, lifetime risky alcohol consumption has generally decreased (Figure 2). Since 2010, there has been a trend towards decreased alcohol consumption among young people (24 years old and younger, and in both males and females). This was driven by an increase in abstainers and low levels of drinking (on average, no more than 2 drinks per day). Average daily drinking was particularly reduced in women aged 18-24 years, from 20% in 2007 to 12.8% in 2016; there was a decrease in alcohol consumption in males in the same age group. There has been a significant increase in abstainers among teenagers (12-17 year olds), from 56% in 2007 to 82% in 2016. More than 25% of males aged over 25 years were likely to exceed the recommended drinking levels compared to less than 15% of females. Among women, those aged 40-60 years were the most likely age group to exceed the lifetime alcohol risk guideline⁴.

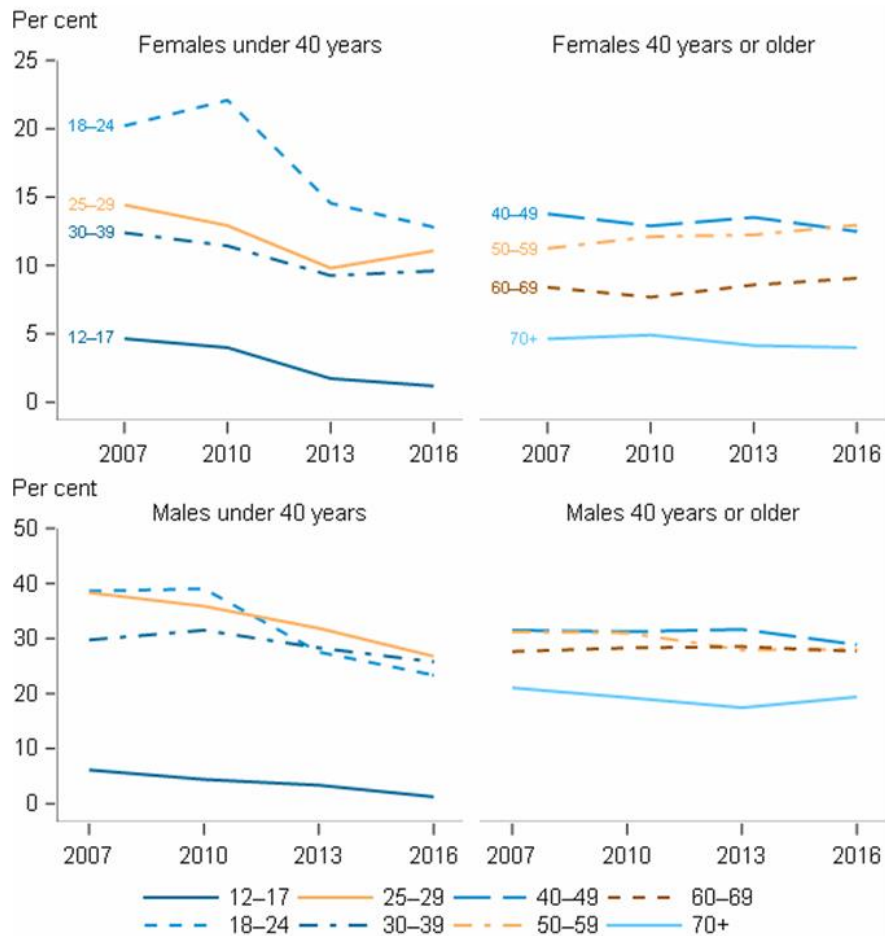


Figure 2 Percentage of females and males exceeding the lifetime risk guidelines, by age

Source: AIHW 2017⁴

Very high-risk drinking, defined as 11 or more standard drinks on one occasion in the last year, decreased from 2010-2016 in people younger than 40 years, especially in people aged 12-17 and 18-24 years. Conversely, an increase in very high-risk drinking was seen in people aged 50-69 (Figure 3).

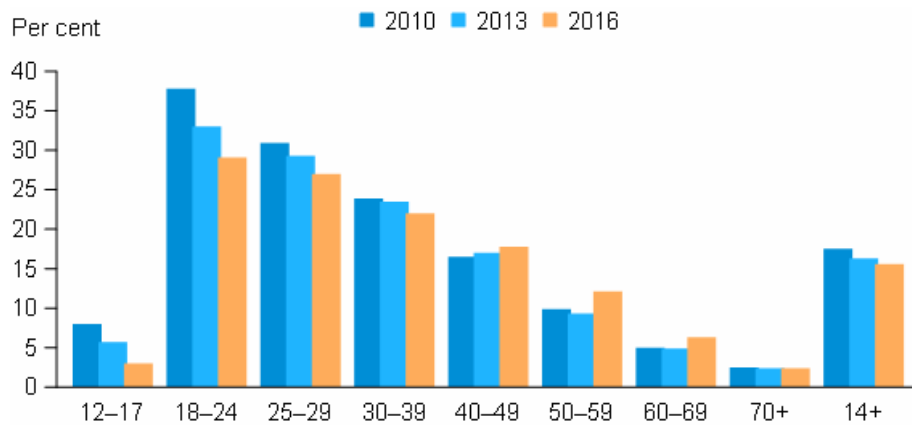
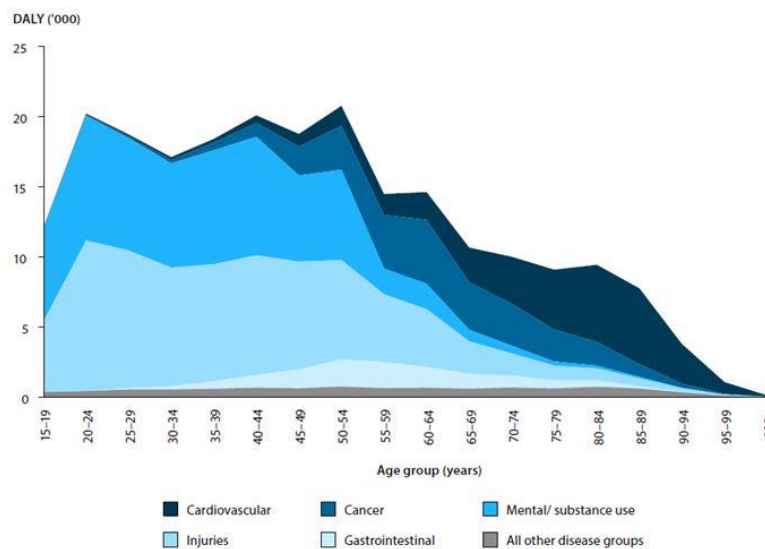


Figure 3 Percentage of very high-risk drinking, by age

Very high-risk drinking was defined as 11 or more drinks consumed at least once in the last year
Source: AIHW 2017⁴

Social and economic consequences

The Australian Burden of Disease Study found that alcohol use was the third leading risk factor contributing to burden of disease and injury in Australia, responsible for 5% of the total burden. The number of DALYs attributable to alcohol use increased from 215,920 in 2003 to 227,666 in 2011². Alcohol use was estimated to contribute to 28% of the burden due to road traffic injuries, 24% of chronic liver disease, 23% of suicide and self-inflicted injuries, 12.2% of mental health disorders, and 10% of pancreatitis burden². Figure 4 illustrates the burden attributable to alcohol across disease and age groups in 2011.



Note: 'All other disease groups' includes infectious diseases, endocrine disorders and neurological conditions.

Figure 4 Burden (DALYs) attributable to alcohol use by age and disease group, 2011

Source: AIHW 2016²

Alcohol is the main drug-related cause of hospital admissions, with the number of admissions increasing from 61,125 in 2010 to 65,668 in 2014 (Figure 5). The rate of

admissions, however, has remained relatively stable between 2010 and 2014 at 280 and 282 hospitalisations per 100,000 population, respectively.

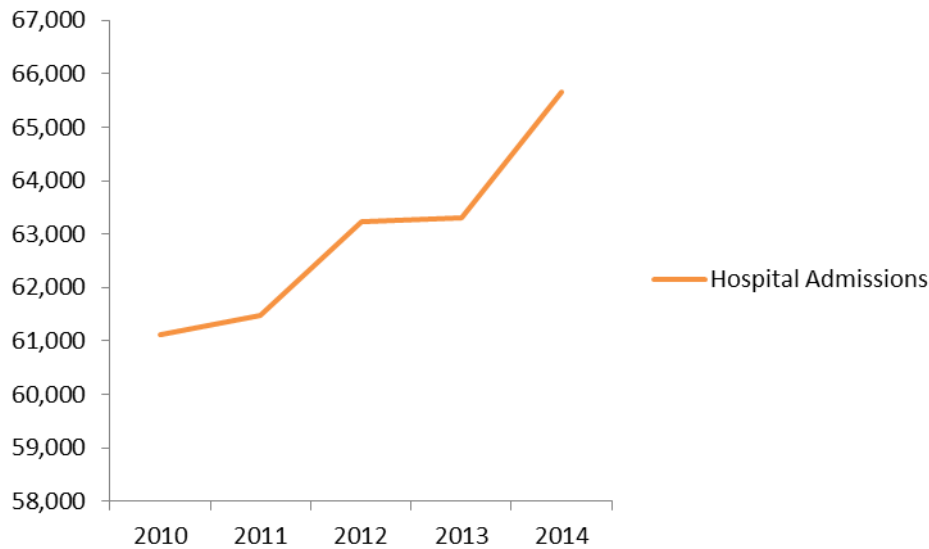


Figure 5 Number of hospital admissions due to alcohol misuse in Australia (2010-2014)

Source: AIHW 2017³

Furthermore, even though alcohol accounts for 38% of treatment episodes related to drug use in Australia¹, treatment rates have decreased across all age groups between 2002 and 2013. Similar to alcohol consumption trends, treatment episodes have particularly decreased in younger people (age groups 14-17 and 18-25 years). The highest levels of treatment due to alcohol misuse occurred in individuals aged 36-45 years (See Figure 6).

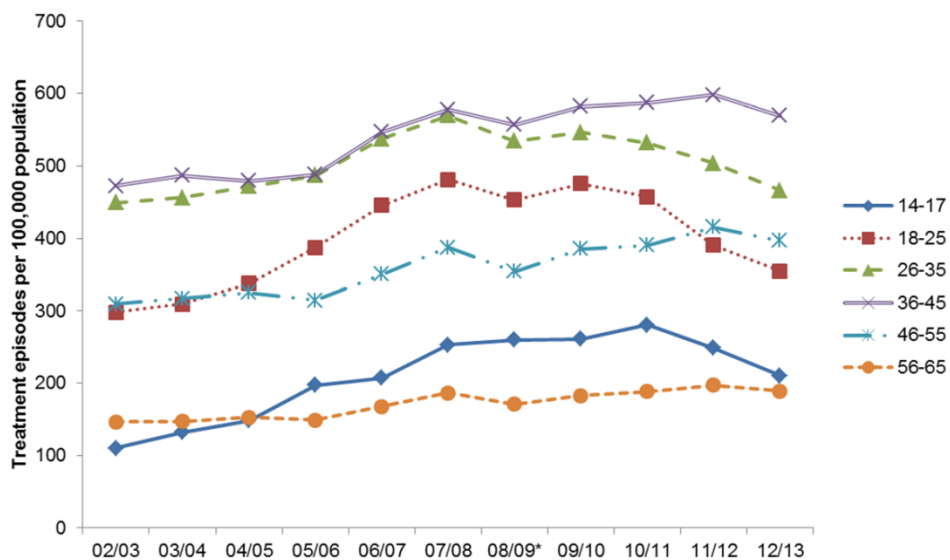


Figure 6 Treatment episodes per 100,000 population due to alcohol misuse by age group, 2003 to 2013

Source: Chan 2016²³

Alcohol-related incidents remain common (reported by 22% of the Australian population), but there is been a decline in the number of people experiencing them, from 4.9 million in 2013 to 4.4 million people in 2016. Among the incidents reported, verbal abuse had the

highest rates, followed by being put in fear by someone under the influence of alcohol, and physical abuse (See Figure 7).

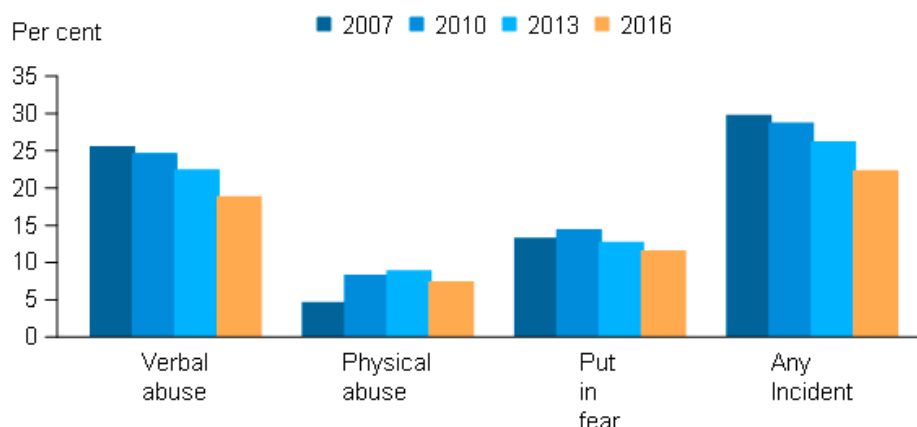


Figure 7 People aged 14 or older experiencing alcohol-related incidents

Source: AIHW 2017⁴

Alcohol use also represents a significant financial burden to society. In 2010, the total cost of alcohol-related problems in Australia was over \$14 billion, of which almost \$3 billion were attributed to criminal justice costs, \$1.7 billion to health system costs, \$6 billion due to productivity losses, and \$3.7 billion associated with traffic accidents⁷³.

Current guidance for alcohol consumption in Australia

The 2009 Alcohol Guidelines⁸³ provided universal guidance applicable to healthy adults aged 18 years and over (Guidelines 1 and 2), guidance specific to children and young people (Guideline 3), and to pregnant and breastfeeding women (Guideline 4). A summary of the guidelines is presented in Figure 8.

Figure 8 NHMRC Alcohol Guidelines Summary

Guideline 1	Reducing the risk of alcohol-related harm over a lifetime
	<ul style="list-style-type: none"> The lifetime risk of harm from drinking alcohol increases with the amount consumed. For healthy men and women, drinking no more than two standard drinks on any day reduces the lifetime risk of harm from alcohol-related disease or injury.
Guideline 2	Reducing the risk of injury on a single occasion of drinking
	<ul style="list-style-type: none"> On a single occasion of drinking, the risk of alcohol-related injury increases with the amount consumed. For healthy men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury.
Guideline 3	Children and young people under 18 years of age
	<ul style="list-style-type: none"> For children and young people under 18 years of age, not drinking alcohol is the safest option. Parents and carers should be advised that children under 15 years of age are at the greatest risk of harm from drinking and that for this age group, not drinking alcohol is especially important. For young people aged 15-17 years, the safest option is to delay the initiation of drinking for as long as possible.
Guideline 4	Pregnancy and breastfeeding
	<ul style="list-style-type: none"> Maternal alcohol consumption can harm the developing fetus or breastfeeding baby. For women who are pregnant or planning a pregnancy, not drinking is the safest option. For women who are breastfeeding, not drinking is the safest option.

Other Australian health organisations that include alcohol intake recommendations are:

1. NHMRC Australian Dietary Guidelines⁸⁴

Guideline 3 - Limit intake of foods containing saturated fat, added salt, added sugars and alcohol.

- If you choose to drink alcohol, limit intake. For women who are pregnant, planning a pregnancy or breastfeeding, not drinking alcohol is the safest option.

2. The Cancer Council Australia National Cancer Prevention Policy 2007-2009¹³⁰

The Cancer Council:

- aims to increase awareness of the link between alcohol consumption and cancer risk among health authorities, health professionals and the community, and encourage efforts to reduce alcohol consumption; and,
- supports a lower limit for alcohol consumption of limit their average daily intake of alcohol to no more than two standard drinks a day for men and one standard drink a day for women.

3. The National Heart Foundation of Australia^{80, 81}

The National Heart Foundation recommends following NHMRC alcohol guidelines. In addition, the National Heart Foundation states:

- We do not recommend that patients who don't drink start drinking, or that patients who drink increase their alcohol intake. It is also recommended that patients with coronary heart disease (CHD) consume a low-risk amount of alcohol. In particular:
 - Patients with CHD drink no more than two standard drinks per day
 - Women with high blood pressure or who are taking blood pressure medicine should drink no more than one standard drink per day

Comparison with international guidelines

National alcohol policies are developed with the aim of reducing the harmful use of alcohol and the alcohol-attributable health and social burden in a population and in society. National health services play a key role in developing prevention and treatment guidelines¹⁶⁴.

International recommendations on alcohol consumption vary slightly across countries. We have included guidelines from Canada, USA, New Zealand, UK, France, Germany, Italy, and Spain in Figure 9.

Figure 9 International guideline recommendations

Country	Recommended limits (males)	Recommended limits (females)	Standard drink (grams (g) alcohol)	Other recommendations
Canada	<ul style="list-style-type: none"> • 15 drinks a week, with no more than 3 drinks a day • No more than 4 drinks on any single occasion 	<ul style="list-style-type: none"> • 10 drinks a week, with no more than 2 drinks a day • No more than 3 drinks on any single occasion 	13.5	<ul style="list-style-type: none"> • These recommendations equate to up to 207 g/week or 41.4 g/day for men and 138 g/week or 27.6 g/day for women. • A standard drink is 341 mL 5% alcohol beer, cider or cooler; 142 mL 12% alcohol wine; 43 mL 40% distilled alcohol.

Country	Recommended limits (males)	Recommended limits (females)	Standard drink (grams (g) alcohol)	Other recommendations
				<ul style="list-style-type: none"> Teens should speak with their parents about drinking. If they choose to drink, they should do so under parental guidance; never more than 1–2 drinks at a time, and never more than 1–2 times per week. They should plan ahead [and] follow local alcohol laws...
USA	<ul style="list-style-type: none"> Up to 28 g/day Over 60 years old: up to 12 g/day or 84 g/week, never more than 36 g at once Up to 56 g/day on any one day, up to 196 g/week; if aged over 65: up to 42 g on any one day, up to 98 g/week 	<ul style="list-style-type: none"> Up to 14 g/day Over 60 years old: up to 12 g/day or 84 g/week, never more than 24 g at once Up to 42 g on any one day, up to 98 g/week 	14	<ul style="list-style-type: none"> Dietary Guidelines for Americans (2015-2020): If alcohol is consumed, it should be in moderation—up to one drink per day for women and up to two drinks per day for men—and only by adults of legal drinking age... if alcohol is consumed, the calories from alcohol should be accounted for so that the limits on calories for other uses and total calories are not exceeded... High-risk drinking: 56 g or more on any day or 112 g/week or more for women and 70 g or more on any day or 210 g/week or more for men. Binge drinking: consumption within about 2 hours of 56 g or more for women and 70 g or more for men. Excessive alcohol consumption: includes binge drinking, heavy drinking (112 g/week or more for women and 210 g/week or more for men), and any drinking by pregnant women or those under 21 years of age Many individuals should not consume alcohol, including individuals who are taking certain over-the-counter or prescription medications or who have certain medical conditions, those who are recovering from alcoholism or are unable to control the amount they drink, and anyone younger than age 21 years. Individuals should not drink if they are driving, planning to drive, or are participating in other activities requiring skill, coordination, and alertness. National Institute of Alcohol Abuse and Alcoholism: These guidelines are specifically for low risk of developing alcohol use disorders. If you have a health problem or take certain medications, you may need to drink less or not at all.
New Zealand	<ul style="list-style-type: none"> Up to 30 g/day or 150 g/week, or 50 g on one occasion Over 64 years old: 30 g/day, or 150 g/week, or 50 g on one occasion 	<ul style="list-style-type: none"> Up to 20 g/day, or 100 g/week, or 40 g on one occasion Over 64 years old: 20 g/day, or 100g/week, or 40g on one occasion 	10	<ul style="list-style-type: none"> Low-risk is not no-risk. Even when drinking within low-risk limits, a range of factors can affect your level of risk, including the rate of drinking, your body type or genetic makeup, your gender, existing health problems and if you are young or an older person. There are times and circumstances when you should not drink alcohol. It's advisable not to drink if you: <ul style="list-style-type: none"> are pregnant or planning to

Country	Recommended limits (males)	Recommended limits (females)	Standard drink (grams (g) alcohol)	Other recommendations
				<ul style="list-style-type: none"> ○ <i>get pregnant;</i> ○ <i>are on medication that interacts with alcohol;</i> ○ <i>have a condition made worse by drinking alcohol;</i> ○ <i>feel unwell, depressed, tired or cold as alcohol could make things worse;</i> ○ <i>are about to operate machinery or a vehicle or do anything that is risky or requires skill.</i> ● <i>For children and young people under 18 years, not drinking alcohol is the safest option. Those under 15 years of age are at the greatest risk of harm from drinking alcohol and not drinking in this age group is especially important.</i> ● <i>For young people aged 15 to 17 years, the safest option is to delay drinking for as long as possible. If 15 to 17 year olds do drink alcohol, they should be supervised, drink infrequently and at levels usually below and never exceeding the adult daily limits.</i>
UK	Up to 112 g/week	Up to 112 g/week	8	<ul style="list-style-type: none"> ● <i>This applies to adults who drink regularly or frequently, i.e. most weeks. The Chief Medical Officers' guideline for both men and women is that:</i> <ul style="list-style-type: none"> ○ <i>To keep health risks from alcohol to a low level it is safest not to drink more than 14 units a week on a regular basis.</i> ○ <i>If you regularly drink as much as 14 units per week, it is best to spread your drinking evenly over 3 or more days. If you have one or two heavy drinking episodes a week, you increase your risks of death from long term illness and from accidents and injuries.</i> ○ <i>The risk of developing a range of health problems (including cancers of the mouth, throat and breast) increases the more you drink on a regular basis.</i> ○ <i>If you wish to cut down the amount you drink, a good way to help achieve this is to have several drink-free days each week.</i> ● <i>This applies to drinking on any single occasion (not regular drinking, which is covered by the weekly guideline). The Chief Medical Officers' advice for men and women who wish to keep their short</i>

Country	Recommended limits (males)	Recommended limits (females)	Standard drink (grams (g) alcohol)	Other recommendations
				<p><i>term health risks from single occasion drinking episodes to a low level is to reduce them by: limiting the total amount of alcohol you drink on any single occasion, drinking more slowly, drinking with food, and alternating with water, and planning ahead to avoid problems e.g. by making sure you can get home safely or that you have people you trust with you.</i></p> <ul style="list-style-type: none"> • <i>The risks of injury to a person who has been drinking recently have been found to rise between two and five times when 5-7 units (40-56 g) are drunk in a 3-6 hour period.</i> • <i>If you are a regular weekly drinker and you wish to keep both your short- and long-term health risks from drinking low, this single episode drinking advice is also relevant for you.</i>
France	<ul style="list-style-type: none"> • <i>Up to 30 g/day or 40 g on any one occasion</i> • <i>Proposed: up to 20 g/day or 100 g/week</i> 	<ul style="list-style-type: none"> • <i>Up to 20 g/day or 40 g on any one occasion</i> • <i>Proposed: up to 20 g/day or 100 g/week</i> 	10	<ul style="list-style-type: none"> • <i>Proposed:</i> <ul style="list-style-type: none"> ○ <i>There is no alcohol consumption without risk, but only low-risk, medium-risk, and high-risk consumption. Knowing these different levels helps each person to make their decision. What is known is that the health risks related to alcohol consumption over the lifetime increase with the quantity consumed... There isn't a clear level of consumption that allows one to definitively health risks over their lifetime. Nonetheless, experts of Public Health France and the National Cancer Institute attempted to define acceptable risks and proposed a single value for both sexes, expressed in standard drinks.</i> ○ <i>Some days without alcohol each week are recommended, and on each occasion: reduce the total quantity consumed; drink slowly while eating and alternate with drinking water; avoid risky places and activities; ensure you are surrounded by people you trust and can return home safely.</i> ○ <i>In the following situations, it is safest not to drink alcohol at all: During childhood, adolescence, and while</i>

Country	Recommended limits (males)	Recommended limits (females)	Standard drink (grams (g) alcohol)	Other recommendations
				<i>growing; If driving a vehicle; If practicing risky sports; If taking certain medications; In case of certain diseases.</i>
Germany	<i>Up to 24 g/day</i>	<i>Up to 12 g/day</i>	<i>None</i>	<ul style="list-style-type: none"> • <i>Federal Center for Health Education: At least two days of abstinence from alcohol a week are recommended.</i> • <i>German Centre for Addiction Issues: Different consumer classes have been defined in recent years to assess the individual risks. However, there is no completely risk-free alcohol consumption level. A couple of days without alcohol per week are recommended to avoid drinking becoming a habit.</i> • <i>Low-risk consumption: Men: up to 24 g/day, Women: up to 12 g/day</i> • <i>Risky consumption: Men: above 20 to 60 g/day, Women: above 12 to 40 g/day</i> • <i>Dangerous consumption: Men: above 60 to 120 g/day, Women: above 40 to 80 g/day</i> • <i>Over (High)-consumption: Men: above 120 g/day, Women: above 80 g/day.</i>
Italy	<ul style="list-style-type: none"> • <i>Up to 24 g/day if aged 21-65</i> • <i>Up to 12 g/day if aged 18-21 or above 65</i> 	<i>up to 12 g/day</i>	<i>12</i>	<ul style="list-style-type: none"> • <i>There are situations where complete abstinence from alcohol consumption is recommended: If taking medication, suffering from an acute or chronic disease, addicted to alcohol or other substances, fasting or between meals, while on the job, or if you must drive a vehicle or operate machinery, if planning to become pregnant, pregnant, or breastfeeding.</i> • <i>Binge drinking is defined as consuming 72 g or more within 2-3 hours.</i>
Spain	<i>Up to 40 g/day or 280 g/week</i>	<i>Up to 20 g/day or 170 g/week</i>	<i>10</i>	<i>Drinking can always be considered risky in certain circumstances, like: being a minor, driving a vehicle, doing work that requires coordination, concentration and attention, if taking certain medications that may interact with alcohol, if suffering a disease that alcohol could exacerbate.</i>

Source: IARD 2016⁵²

Methodology

The methods underpinning this overview were based on the methodology described in Chapter 22 of the Cochrane Handbook for Systematic Reviews of Interventions⁴⁵ and the Handbook for Grading the Quality of Evidence and the Strength of Recommendations using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach¹¹⁹.

As the overview topic was a public health question rather than a clinical intervention, and methodologies to conduct overviews are developing, NHMRC and CTC developed and agreed upon a new, two-step approach to conduct this overview. The specific methods are detailed below. The aim was to identify the systematic review(s) of the highest methodological quality over-and-above a pre-specified quality threshold for each outcome for each research question.

Developing the review questions and outcomes

The research questions were developed in a Population, Exposure and Outcome (PEO) framework. Note that as the exposure and comparator(s) were varying levels and/or patterns of alcohol consumption, they have been combined into a single element (E) in this framework. These PEO criteria were used for developing the literature search strategies and screening of the identified systematic reviews, and to also guide the use of the GRADE assessment. The review questions and outcomes were specified in the statement of requirement and defined by NHMRC and the Alcohol Working Committee (AWC).

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?

The PEO framework for each research question is presented in Figure 10, Figure 11, Figure 12, and Figure 13.

Figure 10 PEO criteria for the evaluation of research question 1

Element	Criteria
Population	<p>The general population</p> <p>If evidence is identified, the following specific subpopulations will be examined:</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

Figure 11 PEO criteria for the evaluation of research question 2

Element	Criteria
Population	<p>The general population</p> <p>If evidence is identified, the following specific subpopulations will be examined:</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> All-cause mortality and morbidity Cancer (including head and neck, breast, liver, 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

Figure 12 PEO criteria for research question 3

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

Figure 13 PEO criteria for research question 4

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

Literature searches

Comprehensive systematic literature searches were undertaken on 5 January 2017 to identify all systematic reviews published since January 2007 relevant to the review questions. Papers published after this date were not considered for inclusion in the overview. Only one search was undertaken for all questions, as outcomes and population were not included as search terms. Outcomes were not included as search terms because they are often poorly indexed with controlled vocabulary terms in medical databases⁴⁵ which then would result in relevant references would be missed. We searched the following databases using the search strategy in Figure 14:

- 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 Guidelines⁸³, the search was conducted from 1 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.

Figure 14 Search strategy for MEDLINE via Ovid

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

Additionally, a comprehensive search of the grey literature was undertaken on 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/>)
- Centers for Disease Control and Prevention (<https://www.cdc.gov/>)
- World Health Organization (<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/>)

Selection of the evidence

The titles and abstracts of records retrieved by the searches were screened for eligibility by one reviewer, with publications identified as being potentially relevant assessed in full text. These systematic reviews were assessed by 2 reviewers against the PEO criteria (Figure 10, Figure 11, Figure 12, and Figure 13) for the overview in the first instance. Disagreements were resolved through discussion. In addition, populations which were not judged to be relevant to the Australian context were excluded. For example, systematic reviews focused exclusively on a country where there is considered to be a different prevalence of a disease

or systematic reviews that excluded studies other than those done in the country of focus. 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 systematic 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. Only one systematic review was selected for inclusion for each outcome. Details of the assessment of each systematic review assessed in full text are provided in the Technical Report.

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 determine whether it met a threshold for methodological quality. This was identified 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.

Only one systematic review was selected for inclusion for each outcome.

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)¹²¹

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)¹²¹

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)¹²¹

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)¹⁴⁹

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 Technical Report. 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

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 (ROBIS Domain 4: study eligibility criteria¹⁴⁹). 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:

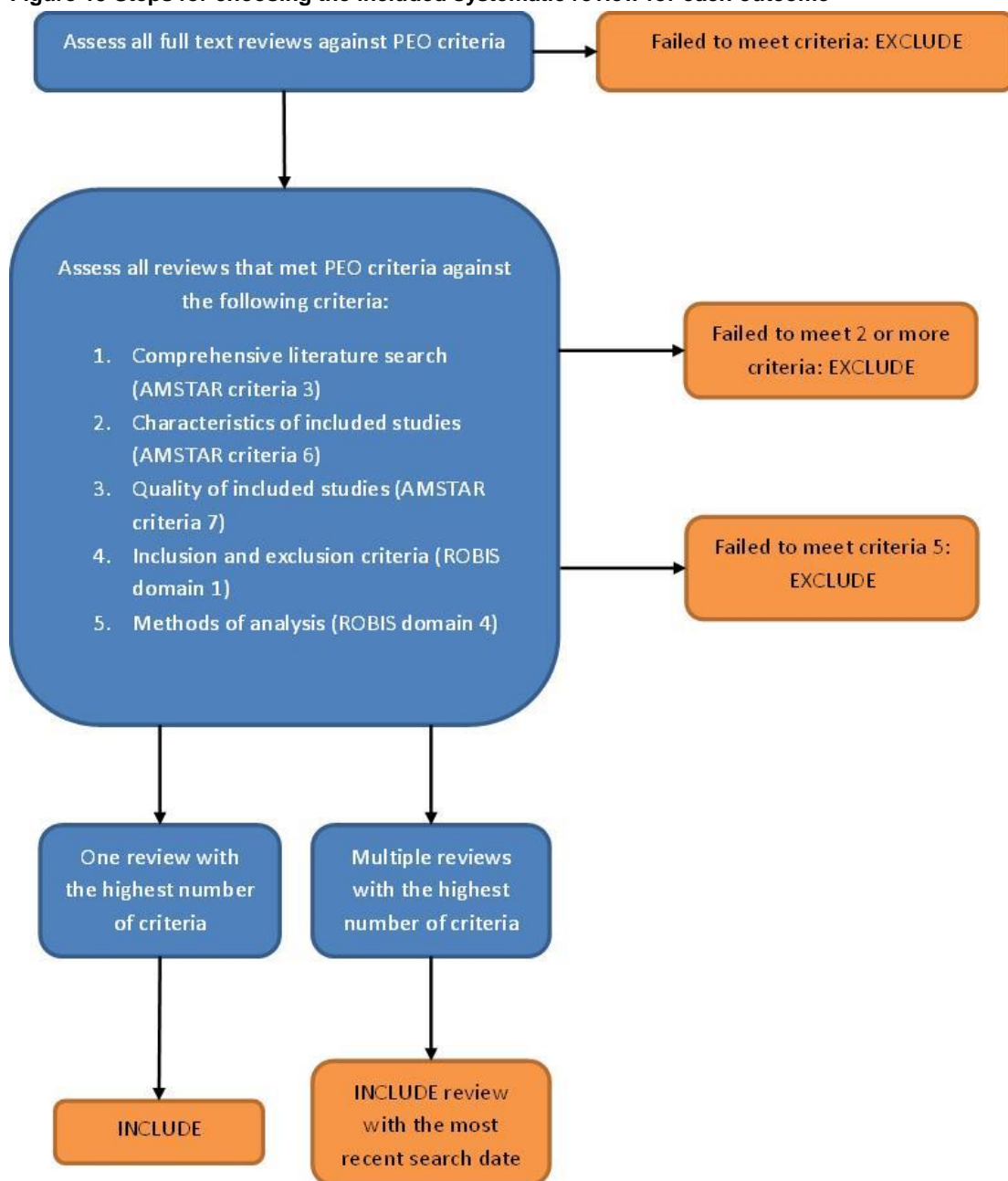
1. They did not provide an adequate description of the methodology used to analyse the studies (any methodology, including narrative syntheses, maybe appropriate). The methods used were not appropriate or adequate justifications for methods of analysis were not provided. If a meta-analysis was performed 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.

A flow chart showing the steps to choosing the systematic review is provided in Figure 15.

Figure 15 Steps for choosing the included systematic review for each outcome



AMSTAR

The reporting quality of all included systematic reviews was assessed using AMSTAR¹¹⁷. This was done by one reviewer and checked by a second reviewer. Any discrepancies in data extraction were resolved by discussion or consultation with a third reviewer (when required).

The AMSTAR tool was used to assess the reporting quality of included systematic reviews. All items were 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. The AMSTAR tool is described in Figure 16.

Figure 16 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

Full details of the AMSTAR assessments for each of the included systematic reviews are available in the Technical Report.

The quality of the systematic reviews according to AMSTAR scores were reported as:

- Poor quality (AMSTAR score < 6);
- Moderate quality (AMSTAR score between 6 and 8);
- Good quality (AMSTAR score >8)

When using AMSTAR to assess included studies we answered 'no' for "6. Were the characteristics of the included studies provided?" if the confounders that were adjusted for were not reported. If the confounders were reported and other characteristics of patients and details such as the measurement of alcohol exposure then this question was answered 'yes'. The protocol stated that the minimum requirement was age, gender, confounders, and levels of alcohol; however, if some of these details were missing but confounders and other characteristics were stated, then this question was still answered 'yes'.

Data Extraction

Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies in data extraction will be resolved by discussion or consultation with a third reviewer (when required). Missing data from individual studies was not sought.

GRADE

Overview of GRADE

The Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach¹⁵ was used to guide assessment of the underlying evidence presented in the systematic reviews.

The evidence for each outcome was assessed using the GRADE system for rating the quality of evidence¹⁵ with some modification for the assessment of a public health intervention⁴². Under the GRADE system, the overall quality of the evidence for an outcome is categorised as high, moderate, low or very low⁴¹. Evidence from randomised controlled trials is initially graded as high quality and evidence from observational studies is initially graded as low quality. On the advice of the NHMRC, and with the approval of the AWC, this overview has adopted the GRADE categorisation suggested by Harder 2015⁴², where observational studies which are less prone to bias are initially graded as 'moderate' as opposed to 'low' quality⁴². Therefore if systematic reviews included prospective cohort studies which were analysed separately from other study designs then these systematic reviews were considered to start at 'moderate' quality.

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 GRADE working group 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.

Figure 17 Factors for downgrading in GRADE

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.

Figure 18 Factors for upgrading in GRADE

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 better differentiate 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 Figure 19 below), however additional limitations may be present.

Figure 19: Potential limitations of observational studies

Potential limitation	Example
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 Hierarchy⁷⁶ 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 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 I^2 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 were 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 review's 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 handbook¹¹⁹: "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 searched 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.

Grading the evidence in practice for this overview

Systematic reviews only including prospective cohort studies started as moderate quality in GRADE. If systematic reviews included study designs other than prospective cohort studies but analysed prospective cohort studies separately, these systematic reviews were also considered to start at moderate.

The protocol stated that if two systematic reviews of the same quality and search date were identified that included different studies, then both systematic reviews would be considered for inclusion. However, as 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. In addition, it is difficult to assess other aspects of GRADE including risk of bias and inconsistency. Therefore we have selected only one systematic review per outcome. For some outcomes there were multiple systematic reviews that met 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 Technical Report 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.

Methodological reviewer comments

The first draft of the overview underwent methodological review by an independent reviewer. The comments and recommendations of the independent reviewer were considered and the overview was revised where relevant.

The key recommendations of the methodological review and the responses are as follows:

- Report the number of reviewers who carried out screening decisions and the process for resolving disagreements.

Response: This has been added to the methodology section of the report.

- Provide a flowchart (or such like) so that a clear outline of the process and decision points for considering inclusion of the reviews is available to the reader.

Response: This has been added to the methodology section of the report.

- Reconsider the inclusion of reviews based on search date (particularly where a low quality systematic review was identified). Undertake AMSTAR assessment for all reviews meeting PEO/study design and minimum criteria and include the highest AMSTAR quality rated review as a priority over search dates.

Response: Further detail on this has been added to the methodology section of the report. The initial assessment of quality used pre-determined selection criteria from both the AMSTAR and ROBIS tools. This is because AMSTAR gives equally weighing to a number of different criteria, however not all criteria would be of equal importance in making a decision about which one to select based on quality. The pre-determined selection criteria were the domains in AMSTAR and ROBIS that were considered to have the most impact of overall quality. These criteria were used to screen the identified reviews initially and then, for each outcome, the review with the highest eligibility score was included in the overview.

- Reconsider the exclusion of reviews based on study type that specify the inclusion of cohort and case-control studies, in addition to cross-sectional and experimental study designs. As a minimum provide a clear justification for the broad application of these criteria across outcomes.

Response: If a systematic review provided findings from cohort/case-control/case-cohort/case-crossover studies separately then it was still considered for inclusion, even if it also included experimental and/or cross-sectional studies. Detail on this has been added to the methodology section.

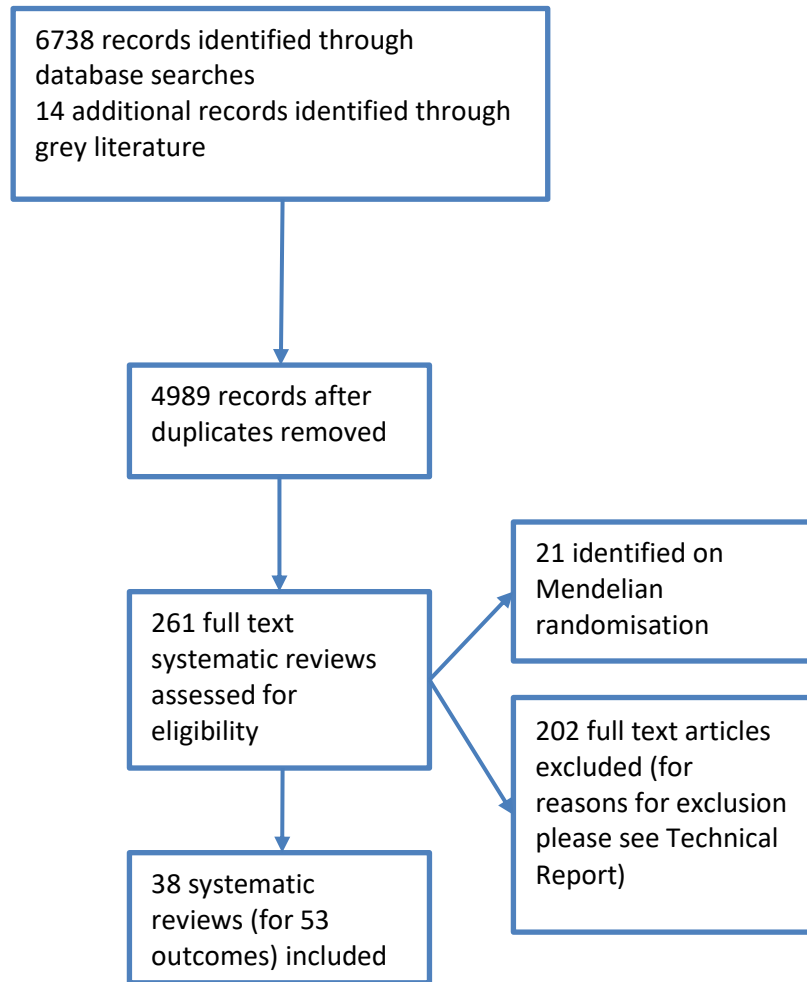
- Evidence statements are not fit for purpose. Apply a consistent approach to constructing technical evidence statements that provides the reader with clear information about the extent and strength of the evidence.

Response: Evidence summaries will be revised in collaboration with NHMRC and the AWC.

Results

The search on multiple databases was conducted on 5 January 2017. After removing duplicate references, we retrieved 4,975 references and an additional 14 references were identified from grey literature searches. Two-hundred and sixty-one full text reviews were assessed for eligibility with 38 systematic reviews fulfilling the eligibility criteria for this overview.

Figure 20 PRISMA Diagram



A list of systematic reviews considered in full text but subsequently excluded from the overview is provided in the Technical Report with reasons for their exclusion.

Question 1: Short term health risks and benefits

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?

Figure 21 Systematic reviews identified at full text for question 1

Importance	Outcomes	Sub-outcomes	No of reviews (SRs) identified at full text*	No of reviews (SRs) included in overview
Critical	Injury to self or others	Domestic violence	4	0
		Suicide	2	0
		Maxillofacial fractures	1	0
		Trauma recidivism	1	0
		Firearm violence	1	0
		Unintentional falls	1	0
		Injury	3	1
		Fatal motor vehicle injury	1	1
	Acute cardiovascular events	Acute cardiovascular events	1	1 reporting 3 outcomes
Important but not critical	Acute exacerbation of a mental illness	Depression	1	0
	Sexually transmitted diseases (STI)	Unprotected sex	3	0
		HIV	1	0
	Harmful alcohol-drug interactions	Opioid overdose	1	0
Sexual function	Erectile dysfunction	1	0	
Of limited importance	Acute GI		No systematic reviews identified	
	Hangover		No systematic reviews identified	

*For full details of reasons for exclusion of systematic reviews please see Technical Report.

Injury to self

Injury

Evidence from 9 case-control and 5 case-crossover studies (n cases=22,182), report an association between any alcohol consumption and increased risk of injury within 6 hours, when compared with non-drinkers.

This is consistent with the conclusions of the other systematic reviews that met the minimum criteria specified in the protocol.

Four systematic reviews^{8, 27, 128, 171} were identified at full text on the association between alcohol consumption and injuries. The systematic review by Zeisser 2013¹⁷¹ was selected for inclusion in the overview because it had the most recent search date and met the minimum criteria specified in the protocol. One other systematic review¹²⁸ met the minimum criteria specified in the protocol, but had a less recent search date. The quality of evidence across the underlying primary studies included in the selected systematic review was assessed as very low quality in GRADE.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 9 case-control and 5 case-crossover studies. No formal quality assessment was undertaken so the risk of bias of individual studies included is unknown; however, the systematic review demonstrates through its analysis and discussion that biases are present due to study design

and recall factors. The systematic review reported that any alcohol consumption was associated with increased risk of injury (OR=2.80 (95% CI 2.21-3.54)) when compared with no alcohol consumption in the 6 hours prior to injury. The odds of injury was raised substantively and significantly for estimates based on different study design types and use of recall measurement, however, heterogeneity was detected and the size of the effect significantly varied according to these factors. The systematic review also reported separately the pooled results for men and women. The summary of findings is presented in Figure 22.

This systematic review did not report the confounders of the included case-control studies or whether or not they did an adjusted or unadjusted analysis. It did report whether gender was adjusted for in the included studies; most of them did not adjust for gender.

This is consistent with the conclusions of the other systematic review¹²⁸ that was identified at full text and met the minimum criteria, which reported that alcohol consumption was associated with an increased risk of injury. This systematic review also reported differences in effect size between study design types. It did not report data on gender separately.

Figure 22 Summary of findings: Injury

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Injury	1 SR ¹⁷¹ (9 Case-control, 5 Case-crossover, n cases=22,182)	One SR including 9 case-control, 5 case-crossover, reported a risk of injury for any alcohol consumption of OR=2.80 (95% CI 2.21-3.54) when compared with no alcohol consumption in the 6 hours prior to injury. The systematic review also reported results separately by study design and recall period. For case-crossover (n=5 studies from 13 results) OR for injury=3.82 (95% CI 2.65-5.50, p=0.00), ED case-control (n=5 studies from 10 results) OR=1.98 (95% CI 1.39-2.82, p=0.00), population case-control (n=4 studies from 4 results) OR=3.15 (95% CI 1.58-6.25, p=0.00). For recall period using usual frequency (n=2 studies from 10 results) OR=4.24 (95% CI 2.541-7.057, p=0.00). For "Yesterday" or "Last week" control (n=12 studies from 17 results) OR=2.32 (95% CI 1.80-3.01 p=0.00).	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Injury **Risk of bias:** No formal quality assessment is undertaken so the risk of bias of individual studies included is unknown, however the systematic review demonstrates through its analysis and discussion that biases are present due to study design and recall factors. **Inconsistency:** Heterogeneity was detected and reported significant differences between study of different design or using different recall factors. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected.

Abbreviations: SR = systematic review; OR = odds ratio; ED = emergency department; CI = confidence interval; n = number of participants

Fatal motor vehicle injury

Evidence from 5 case-control studies (n cases=3272), report a dose-response association between blood alcohol content level and increased risk of fatal motor vehicle injury. Increasing levels of alcohol consumption confer a large increased risk of fatal motor vehicle injury.

One systematic review¹²⁹ was identified at full text on the association between alcohol and fatal motor vehicle injury. The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 5 case-control studies with an unclear risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported alcohol consumption is associated with increased odds of fatal motor vehicle injury. The summary of findings is presented in Figure 23.

A strong dose-response gradient was reported, showing that increased levels of alcohol consumption, measured by increased blood alcohol content (BAC) levels, was associated with increased risk of fatal motor vehicle injury. There was also a large effect size: for a BAC of 0.08 there was a 13 times greater odds of a fatal motor vehicle injury compared with no blood alcohol.

The systematic review was downgraded for insufficiently exploring heterogeneity. Considerable heterogeneity ($I^2 = 99.4\%$) was detected and, as such, the pooled odds ratios should be interpreted with caution because the effect size may be overestimated. However, all of the included studies' effect sizes and corresponding confidence intervals report alcohol consumption to be associated with fatal motor vehicle injury, with very large effect sizes for higher levels of alcohol consumption, that if overestimated would likely still be a large effect.

Figure 23 Summary of findings: Fatal motor vehicle injury

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Fatal motor vehicle injury	1 SR ¹²⁹ (5 case-control, cases n=3272, control n=96,657)	One SR, including 5 case-control studies with an unknown risk of bias, reported OR = 1.74 (95% CI: 1.43–2.14) for every 0.02% increase in BAC, in a random effects meta-analysis. A dose response analysis was also undertaken that reported that at a BAC level of 0.08 OR = 13.0 (95% CI: 11.1–15.2) compared with no blood alcohol. At a BAC level of 0.02 OR = 3.64 (95% CI: 3.37–3.94) (p number for dose-response analysis not reported in the systematic review).	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Effect size: +1	⊕○○○

GRADE reasons for downgrading or upgrading:

Motor vehicle injury **Risk of bias:** Included studies at unknown risk of bias. **Inconsistency:** Heterogeneity detected but reasons for heterogeneity not explored. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Detected. **Dose response:** Detected. **Effect size:** Large.

Abbreviations: BAC = blood alcohol content; SR = systematic review; OR = odds ratio; CI = confidence interval; n = number of participants

Acute cardiovascular events

Myocardial infarction (MI) or Coronary event

Evidence from 4 case-control and 5 case-crossover (n cases=17,966), report a U-shaped dose-response association between alcohol consumption in the previous 24 hours and MI or coronary event.

Ischaemic stroke

Evidence from 8 case-control and 1 case-crossover (n cases=2,599), report a dose-response association between alcohol consumption and ischaemic stroke. This association indicates a linear dose-response within 24 hours and a U-shaped dose-response association within 1 week, for risk of ischaemic stroke.

Haemorrhagic stroke

Evidence from 6 case-control and 1 case-crossover study (n cases=1,262), report a dose-response association between alcohol consumption and haemorrhagic stroke. This association indicates a U-shaped dose-response within 24 hours and a linear dose-response association within 1 week, for risk of haemorrhagic stroke.

One systematic review⁷⁹ was identified at full text on the association between acute alcohol consumption and risk of MI or a major coronary event, ischaemic and hemorrhagic stroke. The systematic review was of poor quality (AMSTAR rating 5 out of 11) and included 16 case-control and 7 case-crossover studies with an unclear risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a U-shaped association between alcohol consumption and acute cardiovascular events (MI, coronary event, ischaemic and hemorrhagic stroke). It reports that there may be a lower risk of acute cardiovascular events for low levels of alcohol consumption, but a higher risk for higher levels of alcohol consumption, compared to no alcohol consumption.

The systematic review included case-control studies. All adjusted for confounders, but the confounders adjusted for varied widely between studies, with some studies only adjusting for age and sex. Only 6 studies adjusted for usual alcohol intake in their analyses. The case-crossover studies and 2 case-control studies were restricted to current drinkers only, however the remaining 14 case-control studies may have included former drinkers in the non-drinking group. There was no separate analysis of studies that included only current drinkers.

Figure 24 Summary of findings: MI or Coronary event

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
MI or Coronary event	1 SR ⁷⁹ (4 Case-control, 5 Case-crossover, n cases=17,966)	One SR reported a U-shaped association between alcohol intake and MI or coronary event (Pcurve<0.001) (5 case-crossover, 3 case-control). It reported a lower risk for alcohol intake of ≈28 g of alcohol in 1 day (RR=0.67) but a higher risk for ≈108 g in 1 day (RR=1.59) for the risk of MI or a major coronary event (I ² =3.3%). The systematic review also reported an RR=0.81 (95% CI 0.70-0.94) for any alcohol consumption compared to no drinking, but with significant heterogeneity (I ² =75.7%) (3 case-crossover, 2 case-control studies).	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○
Ischaemic stroke (IS)	1 SR ⁷⁹ (8 Case-control, 1 Case-crossover, n cases=2,599)	One SR reported a 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 (I ² =8.6%). A dose-response relationship was reported for IS within 24 hours (Pcurve=0.03, Plinearity=0.52). The systematic review also reported 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 (I ² =48.6%, I ² =36.8%, respectively).	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Haemorrhagic stroke (HS)	1 SR ⁷⁹ (6 Case-control, 1 Case-crossover, n cases=1,262)	One SR reported a 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 (I ² =90.5%). A dose-response relationship was reported for HS within one week (Pcurve<0.001, Plinearity=0.42, I ² =8.3%). The systematic review also reported a 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 (I ² =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 of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

MI or coronary event **Risk of bias:** Included studies at unknown risk of bias. **Inconsistency:** Considerable heterogeneity was detected and insufficiently explored. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected.

Ischaemic stroke **Risk of bias:** Included studies at unknown risk of bias. **Inconsistency:** Moderate heterogeneity detected and insufficiently explored. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected.

Haemorrhagic stroke **Risk of bias:** Included studies at unknown risk of bias. **Inconsistency:** Wide CIs. **Indirectness:** Nil. **Imprecision:** 95% CI for 24 hours cross the line of no effect. **Publication bias:** None detected.

Abbreviations: n = number of participants; SR = systematic review; RR=relative risk; CI = confidence interval; HS = haemorrhagic stroke; IS = ischaemic stroke; MI = myocardial infarction; g = grams

Question 2: Long term health risks and benefits

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?

Figure 25 Systematic reviews identified at full text for question 2

Importance	Outcomes	Sub-outcomes	No of reviews (SRs) identified at full text*	No of reviews (SRs) included in overview	
Critical	All-cause mortality	All-cause mortality	7	1	
	All-cause morbidity		No systematic reviews identified		
	All Cancers		Bladder	5	1
			Brain	3	1
			Breast	7	1
			Cervical	2	1
			Colorectal	12	1
			Endometrial	7	1
			Gallbladder	4	1
			Kidney	6	1
			Liver	6	1
			Lung	5	1
			Hodgkin's lymphoma	2	1
			Non-Hodgkin's lymphoma	2	1
			Leukaemia	1	1
			Myeloma	2	1
			Melanoma	2	1
			Mouth, pharynx and larynx	9	1
			Oesophageal	7	1
			Ovarian	6	1
			Pancreatic	7	1
			Prostate	5	1
			Stomach	5	1
	Thyroid	4	1		
	Other	3	0		
	Cardiovascular disease		Coronary heart disease	12	1
			Atrial fibrillation	2	1
			Heart failure	2	1
			Stroke	3	1
Hypertension			2	1	
Other			5	0	
Liver disease		Fatty liver disease	3	0	
		Cirrhosis	1	1	
Alcohol related pancreatitis		Pancreatitis	2	1	

Importance	Outcomes	Sub-outcomes	No of reviews (SRs) identified at full text*	No of reviews (SRs) included in overview
	Mental health disorders	Post-traumatic stress disorder	1	0
		Depression	2	0
	Alcohol use disorders/dependence/withdrawal syndrome		No systematic reviews identified	
	Diabetes and insulin resistance	Diabetes	4	1
	Obesity/overweight	Obesity/body weight	2	0
Important but not critical	Quality of life		No systematic reviews identified	
	Sleep disorders		No systematic reviews identified	
	Central neurological disorders	Multiple sclerosis	1	0
		Amyotrophic lateral sclerosis (ALS)	1	0
		Parkinson's disease	3	0
		Dementia/cognitive decline	13	1
		Seizures	2	1
	Fertility	Fertility (women)	1	0
		Semen quality	1	0
	Osteoporosis	Hip fracture	5	1
	Gout	Gout	2	1
	Thiamine deficiency		No systematic reviews identified	
	Of limited importance	Peripheral neurological disorders		No systematic reviews identified
Reflux			No systematic reviews identified	
Respiratory diseases		Pneumonia	1	1
		Tuberculosis	2	1
Hormonal disorders			No systematic reviews identified	

*For full details of reasons for exclusion of systematic reviews please see Technical Report.

Liver disease: Cirrhosis

Evidence from 14 cohort (n=1,475,765) and 3 case-control studies (n=2,122), report a dose-response association between chronic alcohol consumption and liver cirrhosis, when compared with lifetime abstainers. This association indicates that higher levels of alcohol consumption confer a large increase in risk of liver cirrhosis.

One systematic review¹⁰¹ of poor quality (AMSTAR rating 3 out of 11) was identified at full text on the association between alcohol consumption and liver cirrhosis. It included 14 cohort (n=1,475,765) and 3 case-control studies (n=2,122). The quality of evidence across the underlying primary studies included in the systematic review was assessed as low quality in GRADE.

A dose-response meta-analysis reported that the higher the level of alcohol intake, the greater the risk of morbidity and mortality from liver cirrhosis, in both men and women. A categorical random effects meta-analysis reported that for alcohol consumption < 24g there may be a decreased risk in men for morbidity for liver cirrhosis when compared to lifetime

abstainers (RR 0.3, 95% 0.2 to 0.4); however, at higher levels there is an increased risk of morbidity (>25-36 g: RR 0.7, 95% CI 0.5 to 1.0); >36-48 g: RR 2.0 (95% 1.5 to 2.7). For women, risk was similar at < 24g/day when compared to lifetime abstinence (RR 1.0, 95% 0.5 to 1.9). It should be noted that there were fewer studies that reported on the outcome of morbidity of liver cirrhosis than mortality. For mortality from liver cirrhosis in women, risk was higher at any level, and for men risk was higher at >12g/day, but similar for <12g/day, when compared to lifetime abstainers.

Results from categorical meta-analysis reported there was also large effect sizes for higher levels of alcohol consumption >60g/day on risk of mortality from liver cirrhosis (women RR=22.7 (95% CI 17.2-30.1); men RR=14 (95% CI 11.7-16.7)). Whether or not effect measures were included from unadjusted or adjusted analyses and what confounders were adjusted for in the included studies was not reported.

The risk of bias was unknown as no formal risk of bias assessment of included studies was conducted. Considerable heterogeneity was detected in an initial analysis ($I^2=72%$ women, $I^2=78%$ men) that examined mortality and morbidity combined and it was determined that the outcomes should be analysed separately; however, measurement of subsequent statistical heterogeneity was not reported.

The systematic review applied the following rules for effect measures used:

- In studies that reported results only for both genders combined, the same result was used in each of the meta-analyses for men and women.
- In studies that reported results only for both morbidity and mortality combined, the same result was used in each of the meta-analyses for morbidity and mortality.

Sensitivity analyses were conducted, where the studies that only reported combined results (as above) were excluded from the meta-analyses; however, the systematic review reported the results were similar (no effect measures were reported for the sensitivity analyses).

The systematic review used lifetime abstainers as the reference group. When current abstainers were reported, then the systematic review estimated the proportion of lifetime abstainers based on a previously determined ratio of former drinkers and adjusted the corresponding RRs accordingly. This ratio was calculated based on the studies that used lifetime abstainers as the reference group. This was done to limit any bias that may be introduced by having former drinkers included in the non-drinking reference group. The systematic review also limited inclusion criteria to studies that included 3 or more categories of alcohol consumption only.

Figure 26 Summary of findings: Cirrhosis

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Liver cirrhosis (morbidity and mortality)	1 SR ¹⁰¹ (14 cohort (n=1,475,765), 3 case-control (n=2,122))	<p>One SR with an unknown risk of bias reported in a dose-response meta-analysis that the higher the level of alcohol intake, the greater the risk of morbidity and mortality from liver cirrhosis.</p> <p>In the dose-response meta-analysis mortality for women consuming 24g/day of alcohol RR=4.9 (95% CI 4.0, 6.2) and for 60g/day RR=12.5 (95% CI 8.8, 17.7) compared to lifetime abstinence. For morbidity for women consuming 24g/day of alcohol RR=3.2 (95% CI 2.6, 3.9) and for 60g/day of alcohol RR=6.2 (95% CI 4.4, 8.7). A similar but less distinct association were reported for men (in a figure only so effect sizes were not extractable; p number for dose-response analysis not reported in the systematic review).</p> <p>Results from categorical meta-analysis reported RR=22.7 (95% CI 17.2-30.1) for women and RR=14 (95% CI 11.7-16.7) for men, for alcohol consumption >60g/day for risk of mortality from liver cirrhosis. For alcohol consumption of 12-24g/day RR=5.6 (95% CI 4.5-6.9) for women and RR=1.6 (95% CI 1.4-2.0) for risk of mortality from liver cirrhosis.</p> <p>Results from categorical meta-analysis reported RR=6.1 (95% CI 4.6-8.0) for women and RR=5.0 (95% CI 3.9-6.4) for men, for alcohol consumption >60g/day for risk of morbidity from liver cirrhosis.</p>	<p>Risk of bias: -1</p> <p>Inconsistency: -2</p> <p>Indirectness: 0</p> <p>Imprecision: 0</p> <p>Publication bias: 0</p> <p>Dose response: +1</p> <p>Effect size: +1</p>	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Liver cirrhosis (morbidity and mortality) **Risk of bias:** Included studies at unknown risk of bias. Less than 25% of participants from case-control studies. **Inconsistency:** Heterogeneity detected and insufficiently explored and reported. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected. **Dose response:** Detected. **Effect size:** Large

Abbreviations: n = number of participants; SR = systematic review; RR = risk ratios, relative risk and hazard ratios; g = grams

Cardiovascular diseases

Stroke

Ischaemic stroke

Evidence from 25 prospective cohort studies (n cases=19,302), report a J-shaped association between chronic alcohol consumption and ischaemic stroke, when compared with non-drinkers, never drinkers, or occasional drinkers. This association indicates that at less than 2 drinks per day there is a small decreased risk of ischaemic stroke, however there is an increased risk beyond this amount of consumption.

This is consistent with the conclusions of the 3 other systematic reviews that met the minimum criteria specified in the protocol, which reported either a small decreased risk or no difference in risk for low levels of alcohol consumption.

Intracerebral haemorrhage

Evidence from 11 prospective cohort studies (n cases=2,359), report an association between chronic alcohol consumption and intracerebral haemorrhage, when compared with non-drinkers, never drinkers, or occasional drinkers. This association indicates that at less than 4 drinks per day there is no difference in risk of intracerebral haemorrhage, however there is an increased risk beyond this amount of consumption.

This is consistent with the conclusions of the 3 other systematic reviews that met the minimum criteria specified in the protocol, which reported either a small decreased risk or no difference in risk for low levels of alcohol consumption.

Subarachnoid haemorrhage

Evidence from 11 prospective cohort studies (n cases=1164), report an association between chronic alcohol consumption and subarachnoid haemorrhage, when compared with non-drinkers, never drinkers, or occasional drinkers. This association indicates that at less than 4 drinks per day there is no difference in risk of subarachnoid haemorrhage, however there is an increased risk beyond this amount of consumption.

This is consistent with the conclusions of the 3 other systematic reviews that met the minimum criteria specified in the protocol.

Seven systematic reviews^{25, 67, 91, 109, 168, 172, 178} were identified at full text on the association between alcohol consumption and stroke. The systematic review by Larsson 2016⁶⁷ was selected for inclusion in the overview because it had the most recent search date for ischaemic stroke and intracerebral haemorrhage and met the minimum criteria specified in the protocol. Additionally, it reported ischaemic stroke, intracerebral and subarachnoid haemorrhage and restricted to prospective cohort studies. Three other systematic reviews^{109, 168, 178} met the minimum criteria specified in the protocol, but had less recent search dates and were not on all stroke sub-types. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of low quality (AMSTAR rating 5 out of 11) and included 27 prospective cohort studies with a moderate risk of bias. Risk of bias was assessed using the Newcastle Ottawa Scale (NOS)[†] and scores ranged from 4-9 out of 9. The included studies were at a lower risk of bias due to restriction of inclusion to only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. Subgroup analyses was conducted for study quality, comparing <7 NOS and ≥7 NOS, and similar results were reported for ≤2 drinks/day for all stroke types and >2 drinks/day for ischaemic stroke. Differences were observed for >2 drinks/day for intracerebral and subarachnoid haemorrhage with <7 NOS finding no difference compared to the reference group and ≥7 NOS finding an increased risk for >2 drinks/day. The systematic review only included studies with multivariate analysis; however, the confounders adjusted for varied between studies with some studies only adjusting for age and sex. Most of the studies adjusted smoking.

The systematic review reported for ischaemic stroke, a small decreased risk at ≤2 drinks per day, but a small increased risk for >2 drink per day, when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers). For risk of intracerebral haemorrhage and subarachnoid haemorrhage, there was no difference in risk reported for ≤4 drinks/day but an increased risk at >4 drinks/day compared to the reference group (non-drinkers, never drinkers, or occasional drinkers). Summary of findings is presented in Figure 27.

Subgroup analyses were also conducted for reference groups (non-drinkers, never drinkers, or occasional drinkers). No differences were found, except for occasional drinkers compared to low-to-moderate drinking for ischaemic stroke, where no difference between the two groups was found. Subgroup analyses were also carried out for men compared to women, but no statistically significant differences were found. A subgroup analysis was not conducted for different age groups.

Two systematic reviews^{109, 172} reported a decreased risk of stroke and one systematic review¹⁶⁸ reported no difference for low/moderate intake compared to not drinking, but all three systematic reviews reported that higher levels of alcohol consumption resulted in an increased risk of subarachnoid haemorrhage.

[†] a checklist for assessing the potential biases in non-randomised studies

Figure 27 Summary of findings: Stroke

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Ischaemic stroke	1 SR ⁶⁷ (25 prospective cohorts, cases=19,302)	One SR, including 25 prospective cohort studies reported a decreased risk at ≤ 2 drink per day, but an increased risk for > 2 drink per day for ischaemic stroke when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○
Intracerebral haemorrhage	1 SR ⁶⁷ (11 prospective cohorts, cases=2,359)	One SR, including 11 prospective cohort studies reported no difference in risk of intracerebral haemorrhage for ≤ 4 drinks/day but an increased risk at > 4 drinks/day when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○
Subarachnoid haemorrhage	1 SR ⁶⁷ (11 prospective cohorts, cases=1164).	One SR, including 11 prospective cohort studies reported no difference in risk of subarachnoid haemorrhage for ≤ 4 drinks/day but an increased risk at > 4 drinks/day when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Ischaemic stroke **Risk of bias:** Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. **Inconsistency:** Low or none detected. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Small study bias was identified for low alcohol consumption for ischaemic stroke ($P=0.04$) and subarachnoid haemorrhage ($P=0.01$).

Intracerebral haemorrhage **Risk of bias:** Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. **Inconsistency:** Moderate heterogeneity detected. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil.

Subarachnoid haemorrhage **Risk of bias:** Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. **Inconsistency:** Moderate heterogeneity detected. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Small study bias was identified for low alcohol consumption for subarachnoid haemorrhage ($P=0.01$).

Abbreviations: NOS = Newcastle Ottawa Scale SR = systematic review; RR = relative risk; CI = confidence interval

Heart failure

Evidence from 8 prospective cohort studies (n cases=6,211) indicate that at low levels of alcohol consumption there is a small decreased risk of heart failure however there is no difference in risk of heart failure for higher levels of consumption.

Two systematic reviews^{66, 87} were identified at full text on the association between alcohol consumption and heart failure. The systematic review by Larsson 2015⁶⁶ was selected for inclusion in the overview because it had the most recent search date and the other

systematic review⁸⁷ identified did not meet the minimum criteria set in the protocol. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 8 prospective cohort studies with an unknown risk of bias, as no formal risk of bias assessment of included studies was conducted. However, the included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. Only studies with multivariate analysis that adjusted for age as a minimum were included; however, the confounders adjusted for varied between studies. The systematic review also limited inclusion criteria to studies that included 3 or more categories of alcohol consumption only. The included studies only defined the reference group as non-drinkers and therefore former drinkers may have been included.

The systematic review reported in a dose-response analysis that alcohol consumption at ≤ 7 drinks per week, where one drink was assumed to be 12g of alcohol, is associated with a small reduced risk of heart failure incidence (hospitalisation) and/or mortality, while higher levels of alcohol consumption did not report a difference when compared to non-drinkers. Results from the categorical meta-analysis reported that at < 14 drinks per week, RR = 0.85 (95% CI 0.78–0.93) and for ≥ 14 drinks per week, RR = 0.90 (95% CI 0.72–1.13) compared with non-drinkers. Summary of findings is presented in Figure 28.

Figure 28 Summary of findings: Heart failure

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Heart failure (incidence, hospitalisation and/or mortality)	1 SR ⁶⁶ (8 prospective cohorts, n=202,378, cases=6,211)	One SR, including 8 prospective cohort studies with an unknown risk of bias, reported a non-linear dose-response relationship between alcohol consumption and heart failure. A dose-response analysis (P for non-linearity=0.001) reported that compared with non-drinkers the risk of heart failure for 3 drinks per week RR=0.90 (95% CI 0.84–0.96) for 7 drinks per week RR=0.83 (95% CI 0.73–0.95), for 14 drinks per week RR=0.90 (95% CI 0.73–1.10) and for 21 drinks per week RR=1.07 (95% CI 0.77–1.48). One drink was assumed to be 12g of alcohol. In categorical random effects meta-analysis, <14 drinks per week RR=0.85 (95% CI 0.78–0.93; I ² =39.2%) and for ≥14 drinks per week RR=0.90 (95% CI 0.72–1.13; I ² =41.3%).	Risk of bias: -1 Inconsistency: -1 Indirectness: -1 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Heart failure **Risk of bias:** Included studies at unknown risk of bias. **Inconsistency:** Moderate heterogeneity was detected. **Indirectness:** Outcome indirectness due to combining of outcome from both incidence (hospitalisation) and/or mortality. **Imprecision:** Nil. **Publication bias:** None detected.

Abbreviations: SR = systematic review; RR = relative risk; CI = confidence interval; n = number of participants

Atrial fibrillation

Evidence from 7 prospective cohort studies (n cases=11,419), report a dose-response association between chronic alcohol consumption and atrial fibrillation, when compared with lifetime abstainers. This association indicates that increasing levels of alcohol consumption confer an increased risk of atrial fibrillation.

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Three systematic reviews^{62, 65, 116} were identified at full text on the association between alcohol consumption and atrial fibrillation. The systematic review by Larsson 2014⁶⁵ was selected for inclusion in the overview because it had the most recent search date. Although this systematic review only searched PubMed, it had other strengths over the other systematic reviews identified. The review included only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. It also

limited its outcome definition to incidence of atrial fibrillation, as oppose to focusing on mortality or a combined outcome. It also restricted included studies to only those with an exposure of a minimum of 3 different distinct categories of alcohol consumption. Additionally it includes a newer study that has a large sample size (n = 68,848, n cases=6019) and carries the most weighting in the meta-analysis (39.69%). All of the included studies in the systematic review also conducted multivariate analysis, all of which adjusted for age and sex. However, the other variables adjusted for varied between studies.

The systematic review was of poor quality (AMSTAR rating 4 out of 11) 7 cohort studies with an unknown risk of bias, as no formal risk of bias assessment of included studies was conducted, however the review did include only prospective cohort studies. The quality of evidence across the underlying primary studies included in the systematic review was assessed as moderate quality in GRADE. The systematic review reported a dose-response relationship with alcohol consumption and risk of atrial fibrillation. The linear dose-response analysis reported that for every 1 drink (12g ethanol) per day the RR increased by 1.08 (95% CI: 1.06 to 1.10). Summary of findings is presented in Figure 29. A dose response gradient was reported, showing that increased levels of alcohol consumption resulted in an increased risk of atrial fibrillation, resulting in upgrading in GRADE.

This is consistent with the conclusions of the other two systematic reviews^{62, 116} that were identified at full text and met the minimum inclusion criteria, which reported a dose-response relationship, with higher levels of alcohol consumption associated with increased risk of atrial fibrillation.

Figure 29 Summary of findings: Atrial Fibrillation

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Atrial Fibrillation (AF) incidence or atrial flutter	One SR ⁶⁵ (7 prospective cohort, n=198,485, cases=11,419)	One SR, including 7 prospective cohort studies, reported a dose-response relationship between alcohol consumption and risk of AF. 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) (p linearity <0.001).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	⊕⊕⊕○

GRADE reasons for downgrading or upgrading:

Atrial Fibrillation **Risk of bias:** Included studies at unknown risk of bias but limited to prospective cohort studies only. **Inconsistency:** Nil. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected **Dose response:** Detected.

Abbreviations: SR = systematic review; RR = relative risk; AF = atrial fibrillation; CI = confidence interval; g = grams; n = number of participants

Hypertension

Evidence from 16 prospective cohort studies (n cases-unclear), reported an association between chronic alcohol consumption and hypertension, when compared with non-drinkers.

Two systematic reviews^{21, 143} were identified at full text on the association between alcohol consumption and hypertension. The systematic review by Briasoulis 2012²¹ was selected for inclusion in the overview because it was the only one that met the minimum criteria set in the protocol.

The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 16 prospective cohort studies with an unknown risk of bias, as no formal risk of bias assessment of included studies was conducted. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

In women, a small decrease in risk of hypertension was reported for alcohol consumption of <10 g/day. No difference was reported for 11-20 g/day while an increased risk of hypertension was reported with 31-40 g/day of alcohol. Results for > 40g/day in women were not reported. In men, there was no difference in risk from < 10g/day or 11-20g/day of alcohol. However, 31-40g/day and > 50g/day of alcohol was associated with an increased risk of hypertension. Summary of findings is presented in Figure 30.

The review included only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. It also restricted included studies to only those with an exposure of a minimum of 3 different distinct categories of alcohol consumption. However, it should be noted that the systematic review did not restrict included studies to those with multivariate analysis and did not report whether or which confounders were adjusted for in each of the included studies. The systematic review also did not restrict the reference category to lifetime abstainers, therefore former drinkers may be included in the abstainer category. Heterogeneity was detected and was discussed as a limitation of the systematic review; however, there was no exploration of the heterogeneity via any sensitivity or subgroup analyses.

Figure 30 Summary of findings: Hypertension

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Hypertension	1 SR ²¹ (16 prospective cohorts, men =33,904, women =193,752)	<p>One SR, including 16 prospective cohort studies with an unknown risk of bias, reported on the association between alcohol consumption and the risk of hypertension.</p> <p>Random-effects meta-analysis reported that alcohol consumption of 31-40 g/day (RR, 1.77; 95% CI 1.39–2.26; P<.001) and >50 g/day compared with no alcohol consumption (RR=1.61; 95% CI, 1.31–1.87; P<0.001) was associated with an increased risk of hypertension in men. No difference in risk was found for alcohol consumption in men of <10 g/day (RR=1.03; 95% CI, 0.94–1.13; P=.51), 11- 20 g/day (RR=1.15; 95% CI, 0.99–1.33; P=.06), 21- 30 g/day (RR=1.07; 95% CI, 0.86–1.34; P=.54), and 41-50 g/day (RR=1.17; 95% CI, 0.84–1.65; P=.34).</p> <p>In women, a small decrease in risk of hypertension was reported for alcohol consumption of <10 g/day (RR=0.87; 95% CI, 0.82–0.92; P<.001).No difference was reported for 11- 20 g/day (RR=0.9; 95% CI, 0.87–1.04; P=.17) or for 21-30 g /day (RR=1.16; 95% CI, 0.91– 1.46; P=.23). An increased risk was reported for 31-40 g/day (RR=1.19; 95% CI, 1.07–1.32; P=.002).</p>	<p>Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0</p>	⊕○○○

GRADE reasons for downgrading or upgrading:

Hypertension **Risk of bias:** *Included studies at unknown risk of bias but limited inclusion to prospective cohort studies.*
Inconsistency: *Heterogeneity detected but reasons for heterogeneity insufficiently explored.* **Indirectness:** *Nil.* **Imprecision:** *Nil.* **Publication bias:** *None detected.*

Abbreviations: SR = systematic review; CI = confidence interval; RR = relative risk; g = grams

Coronary heart disease (CHD)/Ischaemic heart disease (IHD)

Evidence from 18 prospective cohort studies (n cases=7756), report a J-shaped association between chronic alcohol consumption and CHD, when compared with non-drinkers. This association indicates that low levels of alcohol consumption confer a small decreased risk; however there is no difference in risk of CHD at higher levels of consumption.

This is consistent with the conclusions of the other 8 systematic reviews that met the minimum criteria specified in the protocol.

Eleven systematic reviews (from 13 articles)^{13, 59, 75, 103-105, 107-109, 167, 174, 178} were identified at full text on the association between alcohol consumption and CHD. The systematic review by Yang 2016¹⁶⁷ was selected for inclusion in the overview because it had the most recent search date, and although it did not do quality assessment of the included studies, it limited included studies to prospective cohorts only. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 5 out of 11) and included 13 cohort studies with an unknown risk of bias. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. The systematic review included studies that adjusted for confounders but the confounders adjusted for varied widely between studies, with some studies only adjusting for age and smoking. The reference group was defined as non-drinkers and may have included former drinkers as well as lifetime abstainers.

The systematic review reported in a dose-response analysis a nonlinear association between alcohol consumption and risk of coronary artery disease ($P_{\text{nonlinearity}} < 0.00$). It reported a decreased risk for $\leq 90\text{g/day}$ and no difference in risk for 135g/day of alcohol consumption when compared to non-drinkers. Summary of findings is presented in Figure 31.

The results are similar to the conclusions of the other 8 systematic reviews that were identified at full text and met the minimum criteria for inclusion. It should be noted that the other systematic reviews reported both incidence and mortality from CHD.

A series of systematic reviews by Roerecke^{103-105, 107, 108} reported that:

- former drinkers had an increased risk for IHD mortality but no significant differences for morbidity, when compared with long-term abstainers;
- irregular heavy drinking had an increased risk for IHD morbidity and mortality when compared with regular moderate drinking alone;
- chronic heavy drinking inferred no difference in risk for IHD incidence when compared to lifetime abstainers; and,
- people with alcohol use disorder had an increased risk for IHD morbidity when compared to the general population.

A systematic review by Bagnardi 2008¹³ on CHD incidence and mortality reported a J-shaped association. Two other systematic reviews^{109, 174} reported that low to moderate alcohol consumption is associated with a decreased risk of CHD when compared with non-drinking.

Another systematic review¹⁷⁷, which was not included as it was published after our search date (published May 2017), was identified which examined alcohol consumption and mortality from CHD. The systematic review reported CHD mortality was decreased in alcohol drinkers compared to abstainers. The systematic review conducted stratified analyses and reported there was no association for those aged 55 years or younger at baseline, in higher quality studies, or in studies that adjusted for heart health.

Figure 31 Summary of findings: CHD incidence

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
CHD incidence (including MI, CHD, non-stroke cardiovascular disease, and other coronary events)	1 SR ¹⁶⁷ (13 articles from 18 prospective cohort studies, n=214,340, cases=7756 CHD)	One SR, including 18 prospective cohort studies with an unknown risk of bias reported in a dose-response analysis a nonlinear association between alcohol consumption and risk of CHD (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.	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

CHD incidence **Risk of bias:** *Included studies at unknown risk of bias but limited inclusion on to prospective cohort studies.*
Inconsistency: *Nil. Heterogeneity in the between studies analysis was low $I^2=28.5\%$.* **Indirectness:** *Nil.*
Imprecision: *Nil.* **Publication bias:** *None detected in systematic review but only searched one database.*

Abbreviations: SR = systematic review; CHD = coronary heart disease; MI = myocardial infarction; RR = relative risk; g = grams; n = number of participants

All-cause mortality

Evidence from 87 prospective cohort studies (n cases=unclear), report a J-shaped association between chronic alcohol consumption and all-cause mortality, when all studies were included in the analysis. However, adjustment according to reference groups and study design characteristics results in changes in effect sizes, with higher quality studies, reference groups that included either occasional drinkers or lifetime abstainers, and those that adjust for a larger number of important confounders, less likely to report a benefit for low-volume drinkers.

The J-shaped association is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol. These systematic reviews did not conduct separate analysis according to reference groups and study design characteristics.

Seven systematic reviews^{56, 64, 102, 106, 122, 126, 142} were identified at full text on the association between alcohol consumption and all-cause mortality. The systematic review by Stockwell 2016¹²⁶ was selected for inclusion in the overview because it had the most recent search date and met the minimum criteria specified in the protocol. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 87 prospective cohort studies with an unknown risk of bias as no formal quality assessment was undertaken. However, many study quality factors were considered in the analysis and differences were found in effect sizes between study of different design and quality. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs.

The systematic review reported that without adjustment a J-shaped association was observed between alcohol intake and risk of all-cause mortality. However, many study design characteristics and people included in the reference group resulted in changes to the effect sizes, with higher quality studies, reference groups that included either occasional drinkers or lifetime abstainers, and those that adjust for a larger number of important confounders, less likely to report a benefit for low-volume drinkers. Summary of findings is presented in Figure 32.

The J-shaped association finding was consistent with the conclusions of two other systematic reviews^{56, 102} that were identified at full text. A systematic review by Jayasekara 2014⁵⁶ also reported a J-shaped association for alcohol consumption and risk of all-cause mortality and also noted that methods used within the identified studies varied widely. A systematic review by Roerecke 2013¹⁰² investigated stratified levels of drinking among those with alcohol use disorder and decreased risk for all-cause mortality in those who achieved abstinence or reduced alcohol consumption when compared with those who continued to consume alcohol heavily.

Figure 32 Summary of findings: All-cause mortality

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
All-cause mortality	1 SR ¹²⁶ (87 prospective cohort studies)	<p>One SR, including 87 prospective cohort studies. Analyses were carried out for to investigate potential reference group, confounding and study design and quality biases.</p> <p>A J-shaped association was reported, when no adjustment was undertaken in the analysis. This reported that for <1.3g/day RR=0.84 (95% CI 0.79-0.89), 1.3–24.9g/day RR = 0.86 (95% CI 0.83-0.90) and for former drinkers RR=1.22 (95% CI 1.14-1.31). However, after adjustment for abstainer biases 1.3–24.9g/day RR = 0.97 (95% CI 0.88-1.07).</p> <p>The systematic review concludes that many study design characteristics and people included in the reference group results in changes to the effect sizes, with higher quality studies, reference groups that include either occasional drinkers or lifetime abstainers and those that adjust for a larger number of important confounders, less likely to report lower risk in low-volume drinkers.</p>	<p>Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0</p>	⊕○○○

GRADE reasons for downgrading or upgrading:

All-cause mortality *Risk of bias:* No formal risk assessment was carried out on the included study but many study quality factors were considered in the analysis and differences were found in effect sizes between study of different design and quality. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. *Inconsistency:* Considerable heterogeneity detected. *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* No significant publication bias detected.

Abbreviations: SR = systematic review; RR = relative risk; CI = confidence interval; g = grams

Pancreatitis

Chronic pancreatitis

Evidence from 3 case-control and 2 cohort studies (n cases=unknown), report a dose-response association between chronic alcohol consumption and chronic pancreatitis, when compared with abstainers (including former drinkers). This association indicates higher levels of alcohol consumption confer a large increased risk of risk of chronic pancreatitis.

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Acute pancreatitis

Evidence from 4 case-control and 2 cohort studies (n cases=unknown), reports a dose-response association between chronic alcohol consumption and acute pancreatitis, when compared with abstainers (including former drinkers).

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Three systematic reviews^{7, 53, 118} were identified at full text on the association between alcohol consumption and pancreatitis. The systematic review included was by Samokhvalov 2015¹¹⁸ and was chosen as it was the systematic review with the most recent search date and it was an updated systematic review of Irving 2009⁵³. It also included a more comprehensive dose-response analysis than the systematic review by Alsamarrai 2014⁷. The quality of evidence across the underlying primary studies included in the systematic review was assessed as low quality in GRADE.

The included systematic review¹¹⁸ was of poor quality (AMSTAR rating 3 out of 11) and included 5 case-control and 2 cohort studies with an unknown risk of bias. The systematic review reported a linear dose-response relationship between alcohol consumption and pancreatitis, with increasing levels of alcohol consumption associated with a higher risk of chronic pancreatitis. In men, there was also reported to be a linear dose-response relationship between alcohol and acute pancreatitis. For women, there was a J-shaped association between alcohol consumption and acute pancreatitis. The systematic review also noted that this may be due to former drinkers being included in the abstainer categories. The effect size observed for decreased risk in women at <40g per day is RR=0.76 (95% CI: 0.60-0.97). Summary of findings are presented in Figure 33.

The risk of bias is unknown as no formal risk of bias assessment of included studies was conducted. A dose response gradient was reported, showing that increased levels of alcohol consumption resulted in an increased risk of chronic pancreatitis. A large effect size was reported for higher levels of alcohol consumption (at 100g per day this increased to RR=6.29 (95% CI: 3.04-13.02)).

The systematic review did not restrict included studies to those with multivariate analysis and included studies with both unadjusted and adjusted analyses, which were meta-analysed together. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies.

The findings of the systematic review are consistent with the systematic reviews not selected for inclusion in the overview, which both reported a dose-response relationship between increased alcohol consumption and increased risk of chronic and acute pancreatitis^{7, 53}.

Figure 33 Summary of findings: Pancreatitis

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Pancreatitis (acute and chronic)	1 SR ¹¹⁸ (5 Case-control, 2 Cohort, n=157,026, cases=3,186)	One systematic review with an unknown risk of bias reported a dose-response relationship for alcohol consumption and risk of pancreatitis. For risk of chronic pancreatitis it reported for 25g per day of alcohol a 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.	Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1 Effect size: +1	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Pancreatitis **Risk of bias:** Included studies at unknown risk of bias. Less than 25% of participants from case-control studies. **Inconsistency:** Moderate to high heterogeneity was detected and insufficiently explored. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected. **Dose response:** Detected. **Effect size:** Large.

Abbreviations: n = number of participants; SR = systematic review; CI = confidence interval; g = grams

Type II diabetes

Evidence from 37 cohorts and 1 nested case-control study (n= 1,902,605), report a J-shaped association between alcohol consumption and type II diabetes, when compared with current and lifetime abstainers.

The other systematic reviews that met the minimum criteria specified in the protocol reported that low and moderate alcohol intake resulted in a decreased risk of type II diabetes, but heavy alcohol consumption had no difference in risk compared to current abstainers.

Four systematic reviews^{6, 14, 47, 61} were identified at full text on the association between alcohol consumption and type II diabetes. The systematic review by Knott 2015⁶¹ was selected for inclusion in the overview because it had the most recent search date which met all of the inclusion criteria set in the protocol. Additionally, the included systematic review conducted analyses on the interaction between studies using different referent groups,

comparing those that restricted to lifetime abstainers or only to current abstainers, which may include former drinkers. Two other systematic reviews^{6,14} also met the minimum criteria set in the protocol.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 1 nested case-control and 37 cohort studies with a moderate risk of bias (NOS 3-9, median 6). The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE. The systematic review reported in a dose-response analysis that there is a decreased risk of type II diabetes with alcohol consumption <63 g/day and the risk increases after this level (results only reported in graph and there were no extractable effect sizes), compared to current and lifetime abstainers, with considerable heterogeneity. Summary of findings is presented in Table 32.

The systematic review also noted that this may be due to former drinkers being included the abstainer categories, and therefore they may still carry risk from prior drinking. To investigate, the systematic review conducted analysis on different reference groups (current abstention = 33 studies, lifetime abstention = 5 studies) and reported no risk decrease at any level of alcohol consumption when compared to lifetime abstainers. However, for women a risk decrease was found at <59g/day and the risk increased after this level, when compared to current abstainers.

Sex-stratified analysis across all included studies reported that women had a decreased risk at <71 g/day, but in men there was no decrease in risk even at low levels. This trend was still present when only including lifetime abstainers as the reference group, with a decreased risk at <61 g/day and an increased risk after this level. In men there was no decrease in risk even at low levels.

The included studies are at a lower risk of bias due to restriction of inclusion to only cohort studies and one nested case-control, which are susceptible to the introduction of fewer biases than case-control study designs. Additionally, the systematic review limited inclusion criteria to studies that included 3 or more categories of alcohol consumption only.

The systematic review included studies with multivariable-adjusted analyses (n=24 studies) and unadjusted analyses (n=14 studies), and the confounders adjusted for varied widely between studies. However, when looked at separately, multivariable-adjusted analyses showed a less pronounced decrease in risk than unadjusted analyses at moderate levels of consumption. For exposure reporting there was also variation across the included studies (participant self-report (n = 11 studies), objective ascertainment (n = 21 studies), combination (n = 6 studies)); however, when separate analyses were conducted for these groups there was a greater decrease in risk for objective ascertainment than self-reported exposure.

The systematic review by Baliunas 2009¹⁴ also met the minimum criteria for inclusion as set in the protocol. The systematic review concluded that there is a decreased risk of type II diabetes in men and women who consume moderate amounts of alcohol. However, the included systematic review by Knott 2015⁶¹ (which included a separate sex-stratified analysis of the studies included in Baliunas 2009¹⁴ and newly published studies published since the search date for Baliunas 2009¹⁴) found, for men, that the new studies had no risk decrease for any level of alcohol drinking, whereas the studies included in Baliunas 2009¹⁴ reported a decreased risk for men with moderate levels of alcohol consumption.

The systematic review by Li 2016⁶, also met the minimum criteria set in the protocol and reported that low and moderate alcohol intake resulted in a decreased risk of type II diabetes, but heavy alcohol consumption had no difference in risk compared to current abstainers.

Figure 34 Summary of findings: Diabetes

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Type II diabetes	1 SR ⁶¹ (37 cohort, 1 nested case-control, n=1,902,605)	<p>One SR, including 37 cohort and 1 nested case-control study with a moderate risk of bias, reported in a dose-response analysis a decreased risk of type II diabetes with alcohol consumption <63 g/day, compared to current and lifetime abstainers, with considerable heterogeneity.</p> <p>Stratified and sensitivity analysis were conducted. One was conducted on different referent groups (current abstention = 33 studies, lifetime abstention = 5 studies) and reported no risk decrease at any level of alcohol consumption when compared to lifetime abstainers, but a risk decrease at <59g/day when compared to current abstainers. (P nonlinearity <0.001).</p> <p>Sex-stratified analysis across all included studies reported that women had a decreased risk at <71 g/day, but in men there was no decrease in risk even at low levels. This trend was still present when only including lifetime abstainers as the reference group, with a decreased risk at <61 g/day, but in men there was no decrease in risk even at low levels.</p> <p>For case ascertainment (participant self-report (n = 11), objective ascertainment (n = 21), combination (n = 6)) there was a greater decrease in risk for objective ascertainment than self-reported.</p> <p>For multivariable-adjusted analyses (n=24) compared to unadjusted analyses (n=14), multivariable-adjusted analyses showed a less pronounced decrease in risk than unadjusted analyses at moderate levels of consumption.</p>	<p>Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1</p>	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
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Type II diabetes **Risk of bias:** Included studies at low to high risk of bias (NOS 3-9, median 6). Less than 25% of participants from case-control studies. **Inconsistency:** Considerable heterogeneity detected however stratified and sensitivity analyses were conducted but insufficiently explored heterogeneity. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Potential publication bias reported.

Abbreviations: SR = systematic review; n = number of participants; g = grams

All cancers

Bladder

Evidence from 6 prospective cohorts and 1 retrospective cohort study (n cases=2,673), report no association between chronic alcohol consumption and bladder cancer.

This is consistent with the conclusions of the 4 other systematic reviews that met the minimum criteria specified in the protocol.

Five systematic reviews^{12, 74, 93, 94, 155} were identified at full text on the association between alcohol consumption and bladder cancer. The systematic review conducted by the World Cancer Research Fund 2014a¹⁵⁵ as part of its continuous update project was selected for inclusion in the overview because it had the most recent search date and met the minimum criteria specified in the protocol. It partially met the remaining two criteria (comprehensive literature search and quality assessment) and in both cases justified its approach. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included nine cohort studies and one nested case-control study. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies.

The systematic review reported a summary RR of 0.97 (95% CI: 0.91-1.04, I²=44.6%) per 10g per day increase in alcohol consumption as ethanol. The authors noted evidence of publication bias with the smaller study reporting a stronger positive association. Summary of findings is presented in Figure 35.

This is consistent with the conclusions of the additional four systematic reviews that were identified at full text all of which found no association between alcohol consumption and bladder cancer risk. The review by Bagnardi¹² included case-control studies and searched to September 2012, it found the risk of bladder cancer was RR 0.99 (95% CI: 0.89-1.10, I²=39%) for low, 1.01 (95% CI: 0.91-1.12, I²=41%) for moderate and 0.95 (95% CI: 0.75-1.20, I²=65%) for heavy consumption (19 studies).

Figure 35 Summary of findings: Bladder cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Bladder cancer (incidence/mortality)	1 SR ¹⁵⁵ (6 prospective cohort, 1 retrospective cohort, n=2,673 cases)	One SR, including 6 prospective cohort studies and 1 retrospective cohort study with unknown risk of bias, reported a summary RR of 0.97 (95% CI: 0.91-1.04, I ² =44.6%) per 10g/day increase in ethanol consumption.	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Bladder cancer incidence/mortality: **Risk of bias:** The mostly (8/9) large prospective cohorts studies were at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. **Inconsistency:** Downgraded by 1 due to detection of moderate heterogeneity (I²=44.6%) which was not otherwise explained. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Detected.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval; n = number of participants; g = grams

Brain

Evidence from 4 cohort and 2 case-control studies (n cases=1,808), report no association between chronic alcohol consumption and brain cancer, when compared with non-drinkers.

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Three systematic reviews^{12, 40, 99} were identified at full text on the association between alcohol consumption and brain cancer. Two of the reviews are from the same research group^{12, 40}. The systematic review by Bagnardi 2015¹² was selected for inclusion in the overview because it included analysis across three levels of alcohol consumption in contrast to the review with a more recent search date⁹⁹ which conducted an analysis of drinker versus non-drinker only.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and included 2 case-control and 4 cohort studies with an unknown risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication.

The systematic review reported a summary relative risk of 1.01 (95% CI: 0.86-1.18, I²=6%) for low consumption (≤12.5g per day), 1.10 (95% CI: 0.84-1.43, I²=58%) for moderate consumption (≤50g per day) and 1.45 (95% CI: 0.69-3.08, I²=42%) for heavy (>50g per day) alcohol consumption. Summary of findings is presented in Figure 36.

This is consistent with the conclusions of the two other systematic reviews that were identified at full text, neither of which showed an association between alcohol consumption and brain cancer, although one was from the same research group as the included systematic review.

Figure 36 Summary of findings: Brain cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Brain cancer	1 SR ¹² (4 cohort, 2 case-control, n=1,808 cases)	One SR, including 4 cohort and 2 case-control studies with high risk of bias, reported a summary RR of 1.01 (95% CI: 0.86-1.18, I ² =6%) for low consumption (\leq 12.5g per day), 1.10 (95% CI: 0.84-1.43, I ² =58%) for moderate consumption (\leq 50g per day) and 1.45 (95% CI:0.69-3.08, I ² =42%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Brain cancer **Risk of bias:** Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. The number of participants from case-control or cohort studies is not reported. **Inconsistency:** Moderate heterogeneity detected and not otherwise explained. **Indirectness:** Nil. **Imprecision:** Serious at higher levels of alcohol consumption. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Breast

Breast cancer (post-menopausal)

Evidence from 10 prospective cohorts, 2 case-cohorts and 1 nested case-control study (n cases=10,915), report a dose-response association between chronic alcohol consumption and breast cancer (post-menopausal). This association indicates that increasing levels of alcohol consumption confer an increased risk of breast cancer (post-menopausal).

This is consistent with the conclusions of the other 5 systematic reviews that met the minimum criteria specified in the protocol.

Breast cancer (pre-menopausal)

Evidence from 5 cohort studies (n cases=unclear), report a dose-response association between chronic alcohol consumption and breast cancer (pre-menopausal). This association indicates that increasing levels of alcohol consumption confer an increased risk of breast cancer (pre-menopausal).

This is consistent with the conclusions of the other 5 systematic reviews that met the minimum criteria specified in the protocol.

Seven systematic reviews^{5, 11, 12, 57, 120, 151, 170} were identified at full text on the association between alcohol consumption and breast cancer. The systematic review by WCRF 2010¹⁵¹ was selected for inclusion in the overview. 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. The WCRF review¹⁵¹ has recently been published with convincing evidence that alcohol increases the risk of breast cancer in postmenopausal women. For premenopausal women, the WCRF states that alcohol consumption probably increases the risk of breast cancer. The updated review was not included in this overview as it was published after the search date for the overview.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and conducted separate analyses for premenopausal and postmenopausal breast cancer. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies. Sensitivity analysis was undertaken to explore heterogeneity, including factors related to study quality. The quality of evidence across the underlying primary studies included in the systematic review was assessed as moderate (postmenopausal) and low (premenopausal) quality in GRADE.

For postmenopausal breast cancer the WCRF study¹⁵¹ identified 28 studies of which 13 (10 prospective cohorts, 2 case-cohorts and 1 nested case-control, 10,915 cases) were included in a dose-response meta-analysis. They obtained a summary estimate in the meta-analysis of post-menopausal breast cancer of 1.08 (95% CI: 1.05-1.11) for 10g/day increase in alcohol consumption (13 studies). There was no evidence of substantive heterogeneity between the studies ($I^2=21.0\%$, $P=0.231$) and no indication of any strong influence from each individual study on the summary estimate. The funnel plot did not suggest any publication bias.

The meta-analysis of pre-menopausal breast cancer was not updated because only 1 new prospective cohort was identified. The review therefore reports the meta-analysis from WCRF¹⁵¹ which obtained a summary estimate of 1.09 (95% CI: 1.01-1.17, 5 studies) with significant heterogeneity ($I^2 = 66\%$, possibly explained by differential adjustment for age, anthropometry and genetic factors). The WCRF considers that the evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. Summary of findings is presented in Figure 37.

The WCRF review¹⁵¹ is consistent with the other 5 systematic reviews identified. The most comprehensive is Bagnardi¹² which included 75 case-control and 43 cohort studies with an unknown risk of bias. The systematic review reported a summary relative risk of 1.04 (95% CI: 1.01-1.07, $I^2=63\%$) for low (≤ 12.5 g per day) consumption, 1.23 (95% CI: 1.19-1.28, $I^2=54\%$) for moderate (≤ 50 g per day) consumption and 1.61 (95% CI: 1.33-1.94, $I^2=10\%$) for heavy (>50 g per day) alcohol consumption compared with non-drinkers.

Figure 37 Summary of findings: Breast cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Breast cancer (post-menopausal)	1 SR ¹⁵¹ (10 prospective cohorts, 2 case-cohorts and 1 nested case-control, n=10,915 cases)	1 SR, including 10 prospective cohort, 2 case-cohort and 1 nested-case-control studies with low risk of bias, reported a summary RR of 1.08 (95% CI = 1.05-1.11, I ² =21.0%) per 10g per day increase in alcohol consumption.	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: +1	⊕⊕⊕○
Breast cancer (pre-menopausal)	1 SR ¹⁵¹ (5 cohorts, n=NR)	1 SR, including 5 cohort studies with a low risk of bias, reported a summary RR of 1.09 (95% CI = 1.01-1.17, I ² =66%) per 10g per day increase in alcohol consumption.	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose-response: +1	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Breast cancer – post-menopausal *Risk of bias:* Studies were mostly large prospective cohorts studies where are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. *Inconsistency:* Nil. *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* Nil. *Dose response:* Detected.

Breast cancer – pre-menopausal *Risk of bias:* Studies were mostly large prospective cohorts studies where are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. *Inconsistency:* Moderate heterogeneity detected, partially explained by differential adjustment for age, anthropometry and genetic factors. *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* Nil. *Dose response:* Detected.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval; g = grams; n = number of participants, NR = not reported

Cervical

Evidence from 2 cohort and 3 case-control studies (n=1,588 cases), report no association between chronic alcohol consumption and cervical cancer, when compared with non-drinkers.

One other systematic review met the minimum criteria specified in the protocol and reported that chronic alcohol consumption was associated with a small decreased risk of cervical cancer, but noted that this was possibly due to confounding by several risk factors. It should be noted that the estimates from this systematic review are statistically consistent with those from the systematic review that was selected for inclusion.

Two systematic reviews^{12, 46} were identified at full text on the association between alcohol consumption and cervical cancer. The systematic review by Bagnardi 2015¹² was selected for inclusion in the overview because it included a pooled analysis across two levels of alcohol consumption in contrast to the Hjartaker 2010⁴⁶ review which presented results narratively and met fewer criteria for inclusion.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and included 3 case-control and 2 cohort studies with an unknown risk of bias. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across

multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary relative risk of 0.87 (95% CI: 0.75-1.01, I²=0%) for low consumption (≤12.5g per day), 0.90 (95% CI: 0.73-1.11, I²=7%) for moderate consumption (≤50g per day) and no meta-analysis was possible for heavy (>50g per day) alcohol consumption. Summary of findings is presented in Figure 38.

This finding differs to the conclusions of the Hjartaker 2010⁴⁶ review that identified a possible positive association but noted that this was possibly due to confounding by several risk factors. It should be noted that the estimates from this systematic review are statistically consistent with those from the systematic review that was selected for inclusion.

Figure 38 Summary of findings: Cervical cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Cervical cancer	1 SR ¹² (2 cohort, 3 case-control, n=1,588 cases)	One SR, including 2 cohort and 3 case-control studies with an unknown risk of bias, reported a summary RR of 0.87 (95% CI: 0.75-1.01, I ² =0%) for low consumption (≤12.5g per day) and 0.90 (95% CI: 0.73-1.11, I ² =7%) for moderate consumption compared with non-drinkers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Brain cancer **Risk of bias:** Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. The number of participants from case-control or cohort studies is not reported. **Inconsistency:** Nil. **Indirectness:** Nil. **Imprecision:** Moderate. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Colorectal

Evidence from 7 prospective cohorts and 1 case-cohort study (n cases=5,261), report a dose-response association between chronic alcohol consumption and colorectal cancer. This association indicates that increasing levels of alcohol consumption confer an increased risk of colorectal cancer.

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Twelve systematic reviews^{11, 12, 37, 38, 49, 57, 72, 78, 146, 152, 173, 180} were identified at full text on the association between alcohol consumption and colorectal cancer. The systematic review by

WCRF/AICR¹⁵² was selected for inclusion in the overview because it was the only study which met or partially met all inclusion criteria.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 35 articles reporting on 18 individual cohort studies. Separate analyses were conducted for colorectal, colon and rectal cancer and all results were stratified by sex and geographical region. Risk of bias of the included studies was not assessed; however, the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies. Sensitivity analysis was undertaken to explore heterogeneity, including factors related to study quality. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review included eight studies in the meta-analysis examining colorectal cancer risk (7 prospective cohorts, 1 case-cohort, 5,261 cases) and reported a relative risk of 1.10 (95% CI: 1.06-1.13; $I^2=50.7\%$, $p=0.05$) for 10g/day increase in the consumption of alcohol as ethanol. In analysis stratified by sex, the result remained significant for men (RR= 1.11; 95% CI: 1.08-1.15, $I^2=21.1\%$, $p=0.27$) but not women (RR= 1.07; 95% CI: 0.98-1.17, $I^2=0.0\%$, $p=0.62$). The WCRF has concluded that the evidence that the consumption of more than 30g/day of ethanol from alcoholic drinks is a cause of colorectal cancer is convincing in men, and probably also in women. Summary of findings is presented in Figure 39.

These findings are consistent with the conclusions of the remaining 2 systematic reviews that were identified at full text. For example, the most recent study which conducted analysis by dose reported relative risks of 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 low (≤ 12.5 g/day), moderate (12.6 to 49.9 g/day), and heavy drinking (≥ 50 g/day), respectively¹⁴⁶. Findings from Bagnardi 2015¹² were similar, although no statistically significant effect was observed for low consumption.

Figure 39 Summary of findings: Colorectal cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Colorectal cancer	1 SR ¹⁵² (7 prospective cohorts, 1 case-cohort, n=5,261 cases)	1 SR, including 7 cohort and 1 case-cohort studies with low risk of bias, reported a RR of 1.10 (95% CI = 1.06-1.13; $I^2=50.7\%$, $p=0.05$) for 10g/day increase in the consumption of alcohol as ethanol. For men the RR was 1.11 (95% CI 1.08-1.15, $I^2=21.1\%$, $p=0.27$) and for women the RR was 1.07 (95% CI 0.98-1.17, $I^2=0.0\%$, $p=0.62$) per 10g/day increase in alcohol consumption.	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: +1	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Colorectal cancer **Risk of bias:** Studies were mostly large prospective cohorts studies where are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. **Inconsistency:** Moderate heterogeneity detected. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil. **Dose response:** Detected.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Endometrial

Evidence from 9 cohorts and 1 case-cohort study (n cases=9,766), report no association between chronic alcohol consumption and endometrial cancer, when compared with non-drinkers.

This is consistent with the conclusions of the 6 other systematic reviews that met the minimum criteria specified in the protocol.

Seven systematic reviews^{12, 39, 46, 127, 139, 154, 179} were identified at full text on the association between alcohol consumption and endometrial cancer. The systematic review by Zhou 2016b¹⁷⁹ was selected for inclusion in the overview because was the most recent and met all screening criteria.

The systematic review was of good quality (AMSTAR rating 9 out of 11) and included nine cohort studies and one case-cohort. All were prospective studies and scored between 6 and 8 on the NOS, indicating a low risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as low quality in GRADE.

The systematic review reported a relative risk of 0.95 (95% CI: 0.89–1.01) for moderate alcohol consumption (>1 drink/day) and 1.00 (95% CI: 0.88–1.13) for heavy alcohol consumption (>1 drink/day) compared to non-drinking. In a sensitivity analysis, these estimates were 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. Summary of findings is presented in Figure 40.

This is consistent with the conclusions of the remaining six systematic reviews that were identified at full text. In particular, the WCRF update¹⁵⁴ included nine cohort studies and reported a summary relative risk per 10 g/d of 1.01 (95% CI: 0.97-1.06, I²=29.0%).

Figure 40 Summary of findings: Endometrial cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Endometrial cancer	1 SR ¹⁷⁹ (9 cohort, 1 case-cohort, n=9,766 cases)	1 SR, including 9 cohort and 1 case-cohort study with low risk of bias, reported a RR of 0.95 (95% CI: 0.89–1.01) for moderate alcohol consumption (>1 drink/day) and 1.00 (95% CI: 0.88–1.13) for heavy alcohol consumption (>1 drink/day) compared to non-drinking (p nonlinearity = 0.61).	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Endometrial cancer Risk of bias: Low. Inconsistency: Moderate inconsistency detected, not explained in sensitivity analysis. Indirectness: Nil. Imprecision: Nil. Publication bias: Nil.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Gallbladder

Evidence from 3 cohort studies (n cases=417) is insufficient to make a judgment on the association between alcohol consumption and gallbladder cancer.

This is consistent with the conclusions of the 3 other systematic reviews that met the minimum criteria specified in the protocol. However, 2 of the systematic reviews found an increased risk at higher levels of consumption.

Four systematic reviews^{12, 58, 156, 169} were identified at full text on the association between alcohol consumption and gallbladder cancer. The systematic review conducted by the WCRF 2014b¹⁵⁶ as part of its continuous update project was selected for inclusion in the overview because it had the most recent search date and met four of the six pre-specified inclusion criteria. It partially met the remaining two criteria (comprehensive literature search and quality assessment) and in both cases justified its approach¹⁵⁶.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included three cohort studies. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary RR of 1.07 (95% CI: 0.98-1.17; I²=26.2%) per 10g/day increase of alcohol as ethanol. Summary of findings is presented in Figure 41.

This is broadly consistent with the conclusions of the remaining three studies that were identified at full text, however two of the systematic reviews found an increased risk at higher levels of consumption. This was significant in one (RR 2.64 (95% CI: 1.62-4.30); 8 studies, 'heavy' = >50g/day)¹² and non-significant in the other (1.58 (95% CI: 0.97–2.57); 3 studies, 'heavy' = >14 drinks/week or >80g/day)⁵⁸.

Figure 41 Summary of findings: Gallbladder cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Gallbladder cancer	1 SR ¹⁵⁶ (3 cohort, n=417 cases)	1 SR, including 3 cohort studies with unknown risk of bias, reported a summary RR of 1.07 (95% CI: 0.98-1.17; I ² =26.2%) per 10g/day increase of ethanol.	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Gallbladder cancer **Risk of bias:** Included studies were prospective cohorts which are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment; it was downgraded by 1.
Inconsistency: Nil. **Indirectness:** Nil. **Imprecision:** Downgraded by 1 due to the small number of studies.
Publication bias: no indication of publication bias with Egger's test (p=0.93).

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Kidney

Evidence from 7 cohort studies and 1 pooled analysis (n cases=5,503), reports an association between chronic low levels of alcohol consumption and kidney cancer, compared with non-drinkers. This association indicates that at low levels of alcohol consumption, there is a decreased risk of kidney cancer. Insufficient evidence is available to make any judgment at higher levels of consumption.

This is consistent with the conclusions of the 5 other systematic reviews that met the minimum criteria specified in the protocol.

Six systematic reviews^{12, 17, 26, 124, 165} were identified at full text on the association between alcohol consumption and kidney cancer. The systematic review by Xu 2015¹⁶⁵ was selected for inclusion in the overview because it met all of the pre-specified inclusion criteria and had the most recent search date.

The systematic review was of good quality (AMSTAR rating 9 out of 11) and included seven cohort studies and one pooled analysis of 12 cohort studies. The risk of bias of the included studies was assessed using the NOS and ranged from 6 to 9 (mean 7.5); overall the studies were considered to be at low risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a significant inverse association between alcohol consumption and the risk of kidney cancer for both low (<12.5g/day) (RR=0.92 (95% CI 0.83–1.01, I²= 45.2%, 6 studies) and moderate (12.5-37.5g/day) (RR=0.75 (95% CI 0.66–0.86, I²= 45.1%, 8 studies) consumption, but not heavy consumption 1.08 (>37.5g/day) (95% CI 0.42–2.75, I²= 74.8%, 3 studies) compared with non-drinkers/occasional drinkers . In a dose response analysis the summary relative risk per 5g/day increment was 0.94 (95% CI 0.92–0.95, 8 studies). Summary of findings is presented in Figure 42.

This is consistent with the conclusions of the remaining five systematic reviews that were identified at full text. In particular, the WCRF study¹⁵⁹ found a summary RR per 10 g/d of 0.92 (95% CI: 0.86-0.97; I²= 55.1%). Small study bias was identified with the two smallest studies finding stronger inverse associations. The WCRF made the conclusions that 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.

Figure 42 Summary of findings: Kidney cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Kidney cancer	1 SR ¹⁶⁵ (7 cohort, 1 pooled analysis, n=5,503 cases)	1 SR, including 7 cohort and 1 pooled analysis with low risk of bias, reported summary RR per 5g/day increment was 0.94 (95% CI 0.92–0.95) (P=0.03 for nonlinearity, males only, P=0.05 for nonlinearity).	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Kidney cancer **Risk of bias:** Low. **Inconsistency:** Moderate heterogeneity in categorical analysis not fully explored. **Indirectness:** Nil. **Imprecision:** Few studies at higher levels of exposure, leading to significant imprecision above ~30g/day. **Publication bias:** Nil (note not detected in Xu¹⁶¹ but small study bias was detected in¹⁵⁵, as the GRADE table is for the included study Xu¹⁶¹, this measure was not downgraded).

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Leukaemia

Evidence from 8 cohort (n cases=4,066) and 10 case-control studies (n cases=4,134), report no association between chronic alcohol consumption and leukaemia, when compared with non/occasional drinkers.

One systematic review¹¹³ was identified at full text on the association between alcohol consumption and leukaemia.

The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 10 case-control and 8 cohort studies with an unknown risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE. The systematic review reported a pooled relative risk for leukaemia overall of 0.94 (95% CI: 0.85-1.03) for any alcohol consumption compared to no/occasional consumption. The relative risk for leukaemia overall for low consumption was 0.90 (95%CI: 0.80–1.01) and 0.91 (0.81–1.02) for moderate to heavy consumption compared to no/occasional consumption. The authors also investigated the relative risk by leukaemia subtype (acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, leukaemia not otherwise specified and group (acute, chronic, lymphoid, and myeloid) and found similar findings i.e. no significant association between any alcohol consumption or low or moderate to heavy consumption and the risk of leukaemia.

Summary of findings is presented in Figure 43.

Figure 43 Summary of findings: Leukaemia

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Leukaemia	1 SR ¹¹³ (8 cohort, n=4,066 cases; 10 case-control, n=4,134 cases)	One SR, including 8 cohort and 10 case-control studies with unknown risk of bias, reported a summary RR for leukaemia overall of 0.94 (95% CI: 0.85-1.03, I ² =44.9%) for any alcohol consumption compared to no/occasional consumption. The relative risk for leukaemia overall for low consumption was 0.90 (95%CI: 0.80-1.01, I ² =35.8%) and 0.91 (0.81-1.02, I ² =29.3%) for moderate to heavy consumption compared to no/occasional consumption. Dose-risk meta-regression analysis reported the pooled RR of leukaemia were 0.88 (95%CI: 0.82-0.95) for 12g and 0.90 (95%CI: 0.83-0.99) for 25g and 0.97 (95%CI: 0.84-1.12) for 50g of ethanol per day. Results by subtype found no significant association.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Leukaemia **Risk of bias:** Downgraded by 2 as no assessment of risk of bias was undertaken and case-control studies were included **Inconsistency:** Moderate heterogeneity detected and explored by subgroup and sensitivity analysis however heterogeneity still present in some groups **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil.

Abbreviations: SR = systematic review, ALL= acute lymphocytic leukaemia, CLL = chronic lymphocytic leukaemia, AML = acute myeloid leukaemia, CML = chronic myeloid leukaemia, NOS-LK = leukaemia not otherwise specified

Liver

Evidence from 14 cohort studies (n cases=5,650), report a dose-response association between chronic alcohol consumption and liver cancer. This association indicates higher levels of alcohol consumption confer an increased risk of risk of liver cancer.

This is consistent with the conclusions of the 3 other systematic reviews that met the minimum criteria specified in the protocol.

Six systematic reviews^{12, 28, 44, 88, 138, 160} were identified at full text on the association between alcohol consumption and liver cancer. The systematic review by the World Cancer Research Fund 2015a¹⁶⁰ as part of its continuous update project was selected for inclusion in the overview because it had the most recent search date and met four of the six pre-specified inclusion criteria. It partially met the remaining two criteria (comprehensive literature search and quality assessment) and in both cases justified its approach¹⁶⁰.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 14 cohort studies. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies which are at lower risk of bias compared to case-

control studies. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary RR of 1.04 (95% CI: 1.02-1.06; I²=64.0%) per 10g/day increase of ethanol. Heterogeneity was considered to be largely due to the small size of the effect. The association remained when the analysis was stratified by outcome (incidence/mortality), sex and geographical region. The majority of liver cancer cases have underlying cirrhosis of which chronic excessive alcohol consumption is a known cause. Summary of findings is presented in Figure 44.

These findings are consistent with the conclusions of the remaining studies, three of which directly addressed the research question. All of these three studies undertook categorical meta-analyses with some variation in the findings at low levels of consumption, however above 50g/day or >3 drinks/day all reported statistically significant associations and all the results suggested a strong dose response^{12, 28, 138}.

Figure 44 Summary of findings: Liver cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Liver cancer	1 SR ¹⁶⁰ (14 cohort, n=5,650 cases)	1 SR, including 14 cohort studies with unknown risk of bias, reported a summary RR of 1.04 (95% CI: 1.02-1.06; I ² =64.0%) per 10g of ethanol increase per day in dose-response analysis).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Liver cancer **Risk of bias:** Included studies were prospective cohorts which are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment; it was downgraded by 1. **Inconsistency:** Inconsistency detected (I²=64%) but explained by small effect size. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Detected. **Dose response:** Strong dose response, upgraded by 1.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Lung

Evidence from 18 cohort and 16 case-control studies (n cases=38,423), report no association between chronic alcohol consumption and lung cancer, when compared with non-drinkers.

This is consistent with the conclusions of the 2 other systematic reviews that met the minimum criteria specified in the protocol.

Five systematic reviews^{10, 12, 24, 41, 150} were identified at full text on the association between alcohol consumption and lung cancer. The systematic review by Bagnardi 2015¹² was selected for inclusion in the overview because it met or partially met five of the six pre-specified criteria. Only the WCRF review¹⁵⁰ met more criteria but it was considered to not meet our date criteria as the search was completed in July 2006.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and included 16 case-control and 18 cohort studies with an unknown risk of bias. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across

multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary relative risk of 0.84 (95%CI: 0.79–0.88, I²=44%) for low consumption (≤12.5g per day), 0.98 (95%CI: 0.92–1.05, I²=57%) for moderate consumption (≤50g per day) and 1.15 (95%CI: 1.02–1.30, I²=73%) for heavy (>50g per day) alcohol consumption. The authors note that residual confounding by smoking may have biased the result. Summary of findings is presented in Figure 45.

Of the remaining reviews, one is from the same authors as the included studies and is a study on the association between lung cancer and alcohol consumption in never smokers which found no association¹⁰. Similarly, the WCRF report¹⁵⁰ found no overall association in studies which adjusted for cigarette smoking. The results of the remaining two reviews^{24, 41} are not considered applicable (no meta-analysis or results only provided stratified by type of alcoholic drink).

Figure 45 Summary of findings: Lung cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Lung cancer	1 SR ¹² (18 cohort, 16 case-control, n=38,423 cases)	1 SR, including 18 cohort and 16 case-control studies with unknown risk of bias, reported a summary RR of 0.84 (95%CI: 0.79–0.88, I ² =44%) for low consumption (≤12.5g per day), 0.98 (95%CI: 0.92–1.05, I ² =57%) for moderate consumption (≤50g per day) and 1.15 (95%CI: 1.02–1.30, I ² =73%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Lung cancer **Risk of bias:** Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. The number of participants from case-control or cohort studies is not reported. **Inconsistency:** Moderate heterogeneity detected but reasons for heterogeneity not explored. **Indirectness:** Nil. **Imprecision:** Serious imprecision at higher levels of consumption. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely.

Abbreviations: SR = systematic review RR = relative risk, CI = confidence interval

Lymphoma - Hodgkin's and non-Hodgkin's

Lymphoma - Hodgkin's

Evidence from 2 cohort and 7 case-control studies (n cases=1,335), report an association between chronic alcohol consumption and Hodgkin's lymphoma. This association indicates that alcohol consumption confers a decreased risk of Hodgkin's lymphoma. The results

should be interpreted with caution as the findings could be partially attributable to a misclassification of drinkers among cases, as early symptoms of lymphomas may cause subjects to either quit or reduce their drinking.

This is consistent with the conclusions of the other systematic review that met the minimum criteria specified in the protocol.

Lymphoma - non-Hodgkin's

Evidence from 9 cohort and 15 case-control studies (n cases=14,124), report an association between chronic alcohol consumption and non-Hodgkin's lymphoma.

This is consistent with the conclusions of the other systematic review that met the minimum criteria specified in the protocol.

Two systematic reviews^{12, 135} were identified at full text on the association between alcohol consumption and Hodgkin's lymphoma. The systematic review by Bagnardi 2015¹² was selected for inclusion in the overview because it met or partially met five of the six pre-specified criteria.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and included 2 case-control and 7 cohort studies with an unknown risk of bias. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication.

The systematic review reported a summary relative risk of 0.73 (95%CI: 0.59–0.89, I²=6%) for low consumption (≤ 12.5 g per day), 0.73 (95%CI: 0.60–0.87, I²=0%) for moderate consumption (≤ 50 g per day), and 0.63 (95%CI: 0.41–0.97, I²=0%) for heavy consumption (> 50 g per day). The author's note that the inverse relationship observed could be partially attributable to a misclassification of drinkers among cases, as early symptoms of lymphomas may cause subjects to either quit or reduce their drinking. Summary of findings is presented in Figure 46.

These findings are consistent with the findings of the Tramacere 2012b¹³⁵ review except that a dose-response was not found in Tramacere 2012b. Note that the Tramacere 2012b¹³⁵ review is from the same group as Bagnardi 2015¹².

Two systematic reviews^{12, 134} were identified at full text on the association between alcohol consumption and non-Hodgkin's lymphoma. The systematic review by Bagnardi 2015¹² was selected for inclusion in the overview because it met or partially met five of the six pre-specified criteria.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and included 9 cohort and 15 case-control studies with an unknown risk of bias. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary relative risk of 0.88 (95%CI: 0.80–0.97, I²=65%) for low consumption (≤12.5g per day), 0.87 (95%CI: 0.81–0.95, I²=35%) for moderate consumption (≤50g per day), and 0.75 (95%CI: 0.64–0.88, I²=10%) for heavy consumption (>50g per day).

These findings are consistent with the findings of the Tramacere 2012a¹³⁰ review. Note that the Tramacere 2012a review is from the same group as Bagnardi 2015¹¹.

Figure 46 Summary of findings: Hodgkin’s and non-Hodgkin’s lymphoma

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Hodgkin’s lymphoma	1 SR ¹² (2 cohort ; 7 case-control; n=1,335 total cases)	1 SR, including 2 cohort and 7 case-control studies with unknown risk of bias), reported a summary RR of 0.73 (95%CI: 0.59–0.89, I ² =6%) for low consumption (≤12.5g per day), 0.73 (95%CI: 0.60–0.87, I ² =0%) for moderate consumption (≤50g per day), and 0.63 (95%CI: 0.41–0.97, I ² =0%) for heavy consumption (>50g per day). P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○
non-Hodgkin’s lymphoma	1 SR ¹² (9 cohort; 15 case-control; n=14,124 total cases)	1 SR, including 9 cohort and 15 case-control studies with unknown risk of bias), reported a summary RR of 0.88 (95%CI: 0.80–0.97, I ² =65%) for low consumption (≤12.5g per day), 0.87 (95%CI: 0.81–0.95, I ² =35%) for moderate consumption (≤50g per day), and 0.75 (95%CI: 0.64–0.88, I ² =10%) for heavy consumption (>50g per day). P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Hodgkin’s lymphoma **Risk of bias:** Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. **Inconsistency:** Nil. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely.

non-Hodgkin’s lymphoma **Risk of bias:** Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. **Inconsistency:** Moderate heterogeneity detected but reasons for heterogeneity not explored. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely.

Abbreviations: SR = systematic review RR = relative risk, CI = confidence interval

Melanoma

Evidence from 2 cohort and 14 case-control studies (n cases=6,251 cases), report no association between chronic alcohol consumption and melanoma, when compared with not drinking, in studies that adjusted for sun exposure.

This is consistent with the conclusions of the other systematic reviews that met the minimum criteria specified in the protocol.

Two systematic reviews^{12, 110} were identified at full text on the association between alcohol consumption and melanoma. The two reviews were from the same research group and therefore the systematic review by Rota 2014¹¹⁰ was selected for inclusion in the overview because although it was less recent, it was more comprehensive and included analysis stratified by adjustment for sun exposure, which is considered an important confounder for this outcome.

The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 14 case-control and 2 cohort studies with an unknown risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE. The systematic review reported a summary relative risk of 1.10 (95% CI: 0.96–1.26) for low consumption (<1drink/day) and 1.18 (95% CI: 1.01–1.40) for moderate to heavy consumption (>1 drink/day) compared with no drinking. Summary relative risks at higher levels of consumption were not able to be obtained due to insufficient data. When only studies which adjusted to sun exposure were included the summary relative risk no longer reached statistical significance (1.12, (95% CI: 0.86–1.45)). Summary of findings is presented in Figure 47.

This is consistent with the conclusions of the other study identified at full text; however the two studies are from the same research group.

Figure 47 Summary of findings: Melanoma

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Melanoma	1 SR ¹¹⁰ (2 cohort, 14 case-control, n=6,251 cases)	1 SR, including 2 cohort and 14 case-control studies with unknown risk of bias, reported summary RR of 1.10 (95% CI: 0.96–1.26) for light consumption (<1drink/day) and 1.18 (95% CI: 1.01–1.40) for moderate to heavy consumption (>1 drink/day) compared with no drinking. In studies adjusted for sun exposure, the summary RR was 1.12 (95% CI: 0.86–1.45). P number for dose-response analysis not reported in the systematic review.	Risk of bias: -1 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Melanoma **Risk of bias:** Not assessed and included case-control studies, but less than 25% of the participants from case-control studies. **Inconsistency:** Moderate heterogeneity detected and not explained. **Indirectness:** Downgraded by 1 due to likelihood of residual confounding. **Imprecision:** Serious imprecision. **Publication bias:** Not detected.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Mouth, pharynx and larynx

Mouth and pharynx cancer

Evidence from 5 cohort and 47 case-control studies (n cases=13,895), report a dose-response association between chronic alcohol consumption and mouth and pharynx cancer, when compared with non-drinkers. This association indicates higher levels of alcohol consumption confer a large increased risk of risk of mouth and pharynx cancer.

This is consistent with the conclusions of the 7 other systematic reviews that met the minimum criteria specified in the protocol.

Larynx cancer

Evidence from 3 cohort and 38 case-control studies (n cases=7,059), report a dose-response association between chronic alcohol consumption and larynx cancer, when compared with non-drinkers. This association indicates higher levels of alcohol consumption confer an increased risk of risk of larynx cancer.

This is consistent with the conclusions of the 7 other systematic reviews that met the minimum criteria specified in the protocol.

Nine systematic reviews^{11, 12, 55, 57, 98, 131, 140, 150, 175} were identified at full text which met the PEO criteria on the association between alcohol consumption and cancer of the mouth, pharynx and larynx. The systematic review by the WCRF¹⁵⁰ was the only review to meet or partially meet all pre-specified criteria, however its search date was 2004 and therefore it was considered beyond the search date of this review. Therefore the review by Bagnardi¹² was selected for inclusion in the overview because it met the most criteria of the remaining reviews.

The systematic review was of poor quality (AMSTAR rating 2 out of 11) and analyses mouth and pharynx cancers separately to larynx cancer. Although the quality of the review was poor, the review was a comprehensive review of alcohol and cancer across multiple sites from a group of authors who have published extensively in the area; it is likely that the AMSTAR score, in part, reflects the inability to publish sufficient details in the peer reviewed publication. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

For mouth and pharynx cancer the systematic review included 47 case-control and 5 cohort studies with an unknown risk of bias. The systematic review reported a summary relative risk of 1.13 (95%CI: 1.00–1.26), $I^2=26%$) for low consumption (≤ 12.5 g per day), 1.83 (95%CI: 1.62–2.07), $I^2=72%$) for moderate consumption (≤ 50 g per day) and 5.13 (95%CI: 4.31–6.10), $I^2=77%$) for heavy (>50 g per day) alcohol consumption.

For larynx cancer the systematic review included 38 case-control and 3 cohort studies with an unknown risk of bias. The systematic review reported a summary relative risk of 0.87 (95%CI: 0.68–1.11), $I^2=39%$) for low consumption (≤ 12.5 g per day), 1.44 (95%CI: 1.25–1.66), $I^2=61%$) for moderate consumption (≤ 50 g per day) and 2.65 (95%CI: 2.19–3.19, $I^2=77%$) for heavy (>50 g per day) alcohol consumption. Summary of findings is presented in Figure 48.

This is consistent with the conclusions of the remaining eight studies that were identified at full text. In particular, the WCRF¹⁵⁰ undertook a meta-analysis on two cohort studies, both adjusted for smoking, giving a summary effect estimate of 1.24 (95%CI: 1.18–1.30) per drink/week, with no heterogeneity. The WCRF concluded that the evidence that alcoholic drinks are a cause of mouth, pharynx, and larynx cancers is convincing. They note that

alcohol and tobacco together increase the risk of these cancers more than either acting independently and that no threshold was identified.

Figure 48 Summary of findings: Mouth, pharynx and larynx cancer

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Mouth and pharynx cancer	1 SR ¹² (5 cohort, 47 case-control, n=13,895 cases)	1 SR, including 5 cohort and 47 case-control studies with unknown risk of bias, reported a summary RR of 1.13 (95%CI: 1.00–1.26), I ² =26%) for low consumption (≤12.5g per day), 1.83 (95%CI: 1.62–2.07), I ² =72%) for moderate consumption (≤50g per day) and 5.13 (95%CI: 4.31–6.10), I ² =77%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Large effect: +1	⊕○○○
Larynx cancer	1 SR ¹² (3 cohort, 38 case-control, n=7,059 cases)	1 SR, including 3 cohort and 38 case-control studies with unknown risk of bias, reported a summary RR of 0.87 (95%CI: 0.68–1.11), I ² =39%) for low consumption (≤12.5g per day), 1.44 (95%CI: 1.25–1.66), I ² =61%) for moderate consumption (≤50g per day) and 2.65 (95%CI: 2.19–3.19, I ² =77%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1	⊕○○○

GRADE reasons for downgrading or upgrading:

Mouth and pharynx *Risk of bias:* Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. The number of participants from case-control or cohort studies is not reported. **Inconsistency:** Moderate heterogeneity detected and not otherwise explained. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely. **Dose response:** Detected, therefore upgraded by 1. **Effect size:** Large, therefore upgraded by 1.

Larynx *Risk of bias:* Downgraded by 2 as case-control study design was included and risk of bias was not reported in the SR. The number of participants from case-control or cohort studies is not reported. **Inconsistency:** Moderate heterogeneity detected and not otherwise explained. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** No test undertaken, therefore downgraded by 1 as it is considered likely. **Dose response:** Detected, therefore upgraded by 1.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Multiple myeloma

Evidence from 10 cohort and 16 case-control studies (n cases=7,088), report no association between chronic alcohol consumption and multiple myeloma, compared with non/occasional drinkers.

This is consistent with the conclusions of the other systematic reviews that met the minimum criteria specified in the protocol.

Two systematic reviews^{97, 112} were identified at full text on the association between alcohol consumption and multiple myeloma. The systematic review by Psaltopoulou 2015⁹⁷ was selected for inclusion in the overview because it was the most recent systematic review and met five and partially met one of the six pre-specified criteria.

The systematic review was of poor quality (AMSTAR rating 5 out of 11) and included 16 case-control and 10 cohort studies. The average quality was 7/9 on the NOS with a range of 4 to 8. Sensitivity analysis was undertaken to explore heterogeneity, including factors relating to study quality. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE. The systematic review reported a summary relative risk of 0.88 (95%CI: 0.76 – 1.02, I²=66.4%) from 23 studies for ever or current low consumption (≤12.5g per day), 0.87 (95%CI: 0.77 – 0.99, I²=46.9%) from 24 studies for ever or current moderate consumption (≤50g per day), and 0.86 (95%CI: 0.53 – 1.38, I²=2.6%) from 4 studies for ever or current heavy consumption (>50g per day). Summary of findings is presented in Figure 49. This is consistent with the conclusions of the Rota 2014a systematic review¹¹².

Figure 49 Summary of findings: Multiple myeloma

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Multiple myeloma	1 SR ⁹⁷ (10 cohort; 16 case-control; n=7,088 cases total)	1 SR, including 10 cohort and 16 case-control studies with average quality of 7/9 on the reported a RR of 0.88 (95%CI: 0.76 – 1.02, I ² =66.4%) from 23 studies for ever or current low consumption (≤12.5g per day), 0.87 (95%CI: 0.77 – 0.99, I ² =46.9%) from 24 studies for ever or current moderate consumption (≤50g per day), and 0.86 (95%CI: 0.53 – 1.38, I ² =2.6%) from 4 studies for ever or current heavy consumption (>50g per day).	Risk of bias: 0 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Multiple myeloma Risk of bias: Nil. Inconsistency: heterogeneity detected but reasons for heterogeneity not explored. Indirectness: Nil. Imprecision: Nil. Publication bias: Nil.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Oesophageal

Oesophageal squamous cell carcinoma

Evidence from 4 prospective cohorts, 1 case-cohort and 1 nested case-control study (n cases=unclear), report a dose-response association between chronic alcohol consumption and oesophageal squamous cell carcinoma. This association indicates higher levels of

alcohol consumption confer a large increased risk of risk of oesophageal squamous cell carcinoma.

This is consistent with the conclusions of the 6 other systematic reviews that met the minimum criteria specified in the protocol.

Oesophageal adenocarcinoma

Evidence from 4 prospective cohorts, 1 case-cohort and 1 nested case-control study (n cases=unclear), report no association between chronic alcohol consumption and oesophageal adenocarcinoma.

This is consistent with the conclusions of the 6 other systematic reviews that met the minimum criteria specified in the protocol.

Seven systematic reviews^{11, 12, 54, 57, 69, 133, 161} were identified at full text on the association between alcohol consumption and oesophageal cancer. The systematic review by WCRF 2015¹⁶¹, as part of its continuous update project, was selected for inclusion in the overview because it had the second most recent search date and met four of the six pre-specified inclusion criteria. It partially met the remaining two criteria (comprehensive literature search and quality assessment) and in both cases justified its approach.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 15 cohort studies, 1 case-cohort and 1 nested case-control. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies. The quality of evidence across the underlying primary studies included in the systematic review was assessed as low (oesophageal squamous cell carcinoma) and very low (oesophageal adenocarcinoma) quality in GRADE.

There are two distinct types of oesophageal cancer with different risk factors, squamous cell carcinoma and adenocarcinoma. For squamous cell carcinoma, the systematic review reported a relative risk of 1.25 (95%CI: 1.12-1.41, $I^2 = 95.0\%$, $p < 0.001$) per 10g ethanol/day. The high heterogeneity was not explained in stratified analysis, but was thought to be partly explained by a single study which raised significant risk of bias concerns. When excluding this study the relative risk was 1.30 (95%CI: 1.24, 1.36, $I^2 = 39.3\%$, $p = 0.159$). All studies on squamous cell carcinoma were adjusted for smoking. For adenocarcinoma, the summary relative risk was 1.00 (95%CI: 0.98-1.02, $I^2 = 0.7\%$, $p = 0.41$) per 1 drink/week increase, and all studies, except one, adjusted for BMI or WHR. Summary of findings is presented in Figure 50.

This is consistent with the conclusions of the remaining six systematic reviews that were identified at full text four of which were from the same research group. In particular, Bagnardi¹² reported for oesophageal squamous cell carcinoma a relative risk of 1.26 (95%CI: 1.06–1.50) for low (≤ 12.5 g/day), 2.23 (95%CI: 1.87–2.65) for moderate (≥ 50 g/day) and 4.95 (95%CI: 3.86–6.34) for heavy (> 50 g/day) drinking (54 studies). In a separate paper, the same group reported for oesophageal adenocarcinoma¹³³ relative risks of 0.86 (95%CI: 0.75–0.99) for low (< 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) consumption.

Figure 50 Summary of findings: oesophageal

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Oesophageal squamous cell carcinoma	1 SR ¹⁶¹ (4 prospective cohort, 1 case-cohort and 1 nested case-control, n=NR [†])	1 SR, including 4 prospective cohort, 1 case-cohort and 1 nested case-control studies with unknown risk of bias, reported a RR of 1.25 (1.12-1.41, I ² =95.0%, <0.001) per 10g/day increase in ethanol. Heterogeneity was substantially due to a single low quality study, the RR for analysis excluding this study was 1.30 (1.24, 1.36, I ² = 39.3%, p = 0.159).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Effect size: +1	⊕⊕○○
Oesophageal adenocarcinoma	1 SR ¹⁶¹ (4 prospective cohort, 1 case-cohort and 1 nested case-control, n=NR [†])	1 SR, including 4 prospective cohort, 1 case-cohort and 1 nested case-control studies with unknown risk of bias, reported a RR of 1.00 (0.98-1.02, I ² =0.7%, p=0.41) per 1 drink/week increase. A single study of low quality contributed 90.56% weight, hence the low heterogeneity. When this study was removed the estimate was RR 0.99 (0.92, 1.06, I ² = 20.3%, p = 0.285).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Oesophageal squamous cell carcinoma **Risk of bias:** Studies were mostly large prospective cohorts studies which are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. **Inconsistency:** Heterogeneity observed however substantially explained by a single study. Downgraded by 1 for remaining heterogeneity. **Indirectness:** Nil, all included studies were adjusted for smoking. **Imprecision:** Nil. **Publication bias:** Detected. **Dose response:** Detected. **Effect size:** Large.

[†] Not reported by cancer type. N=6,618 cases for all oesophageal cancers combined.

Oesophageal adenocarcinoma **Risk of bias:** Studies were mostly large prospective cohorts studies which are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. **Inconsistency:** Nil. **Indirectness:** Nil, 5/6 studies adjusted for BMI or WHR. **Imprecision:** Nil. **Publication bias:** Detected.

[†] Not reported by cancer type. N=6,618 cases for all oesophageal cancers combined

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval, BMI = body mass index, WHR = waist to hip ratio; g = grams; n = number of participants; NR = not reported

Ovarian

Evidence from 13 cohort studies (n cases=5,587), report no association between chronic alcohol consumption and ovarian cancer.

This is consistent with the conclusions of the 5 other systematic reviews that met the minimum criteria specified in the protocol.

Six systematic reviews^{12, 46, 60, 111, 157, 166} were identified at full text on the association between alcohol consumption and ovarian cancer. The systematic review by Yan-Hong 2015¹⁶⁶ was selected for inclusion in the overview because it met all pre-specified inclusion criteria and had the most recent search date.

The systematic review was of moderate quality (AMSTAR rating 6 out of 11) and included 13 prospective cohort studies. The risk of bias of the included studies was assessed using the NOS and ranged from 5 to 9 (mean 7.4); overall the studies are considered to be at low risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as low quality in GRADE.

The systematic review reported pooled relative risks of 0.96; (95% CI: 0.93–1.00; $I^2 = 0\%$) for low consumption (<15 g/day), 1.08 (95% CI: 0.92–1.27; $I^2 = 24.4\%$) for moderate consumption (15–30 g/day) and 0.99 (95% CI: 0.88–1.12; $I^2 = 0\%$) for heavy consumption (>30 g/d) compared with non-drinkers. Summary of findings is presented in Figure 51.

This is consistent with the conclusions of the remaining five systematic reviews that were identified at full text none of which found a significant association. In particular, the WCRF¹⁵⁷ in its continuous update project reported a summary relative risk per 10 g/day of 1.01 (95% CI: 0.96-1.06; $I^2 = 7.0\%$) from 8 studies (2,954 cases).

Figure 51 Summary of findings: Ovarian

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Ovarian cancer	1 SR ¹⁶⁶ (13 cohort, n=5,587 cases)	1 SR, including 13 cohort studies with low risk of bias, reported RR of 0.96; (95% CI: 0.93–1.00; $I^2 = 0\%$) for low consumption (<15 g/day), 1.08 (95% CI: 0.92–1.27; $I^2 = 24.4\%$) for moderate consumption (15–30 g/day) and 0.99 (95% CI: 0.88–1.12; $I^2 = 0\%$) for heavy consumption (>30 g/d) compared with non-drinkers.	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Ovarian *Risk of bias:* Low *Inconsistency:* Nil. *Indirectness:* Nil. *Imprecision:* estimates are all non-significant and CI's cross the null, the possibility of either an 8% decreased risk or 24% increased risk remains for moderate consumption *Publication bias:* Nil

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Pancreatic

Evidence from 19 prospective cohort studies (n cases = 11,846), report an association between chronic alcohol consumption and pancreatic cancer, when compared with the lowest alcohol intake level (quantity not specified). The association indicates that low and moderate levels of alcohol consumption confer no difference in risk; however higher levels of alcohol consumption confer a small increased risk of pancreatic cancer.

This is consistent with the conclusions of the other 4 systematic reviews that met the minimum criteria specified in the protocol.

Seven systematic reviews^{7, 12, 43, 71, 136, 147, 153} were identified at full text on the association between alcohol consumption and pancreatic cancer. The systematic review by Wang 2016b¹⁴⁷ was selected for inclusion in the overview because it met all pre-specified inclusion criteria and had the most recent search date.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 19 prospective cohort studies. The risk of bias of the included studies was assessed using the NOS and ranged from 6 to 9 (mean 7.6); overall the studies are considered to be at low risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported pooled relative risks of 0.97 (95 % CI: 0.89–1.05, $I^2=0\%$) for low (0-12g/day), 0.98 (95 % CI: 0.93–1.03, $I^2=0\%$) for moderate (≥ 12 -24 g per day) and 1.15 (95 % CI: 1.06–1.25, $I^2=14.5\%$) for heavy (≥ 24 g per day) alcohol consumption compared with the lowest alcohol intake level (quantity not specified). In dose-response analysis, alcohol intake greater than 15g per day was associated with an increased risk of pancreatic cancer. Summary of findings is presented in Figure 52.

This is consistent with the conclusions of the remaining four systematic reviews that were identified at full text and also met all of the PEO criteria. In particular, the WCRF¹⁵³ 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 but 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)). In dose-response analysis the risk was significant for those consuming 53.4g ethanol or more a day. Note that the threshold for a significant effect is greater in this analysis than that of Wang 2016b¹⁴⁷.

Figure 52 Summary of findings: Pancreatic

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Pancreatic cancer	1 SR ¹⁴⁷ . (19 prospective cohorts, n=11,846 cases)	1 SR, including 19 prospective cohort studies with low risk of bias reported RRs of 0.97 (95 % CI, 0.89–1.05, $I^2=0\%$) for low (0-12g/day), 0.98 (95 % CI: 0.93–1.03, $I^2=0\%$) for moderate (≥ 12 -24 g per day) and 1.15 (95 % CI: 1.06–1.25, $I^2=14.5\%$) for heavy (≥ 24 g per day) alcohol consumption compared with the lowest alcohol intake level (quantity not specified). P nonlinearity = 0.0874	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Pancreatic cancer **Risk of bias:** Low. **Inconsistency:** Downgraded by 1 due to mixed results across consumption levels and unclear dose response curve. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Not detected statistically, but can't be ruled out in funnel plot.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Prostate

Evidence from 16 prospective cohorts, 1 retrospective cohort, 5 hospital-based case-control and 5 population-based case-control studies (n=49,848 cases), report an association between chronic alcohol consumption and prostate cancer, when compared with abstainers, in studies with a fully adjusted analysis. The association indicates that low, moderate and heavy alcohol consumption confers a small increased risk of prostate cancer.

Three other systematic reviews met the minimum criteria specified in the protocol; they reported a small decreased risk or no difference in risk of prostate cancer for alcohol consumption. These systematic reviews did not report results only from studies conducting adjusted analysis.

Five systematic reviews^{12, 77, 114, 158, 176} were identified at full text on the association between alcohol consumption and prostate cancer. The systematic review by Zhao 2016a¹⁷⁶ was selected for inclusion in the overview because it had the most recent search date and met, or partially met, all of the pre-specified inclusion criteria.

The systematic review was of low quality (AMSTAR rating 5 out of 11) and included 16 prospective cohorts, one retrospective cohort, five hospital-based case-control and five population-based case-control studies. No formal quality assessment was undertaken and therefore the studies are considered at unknown risk of bias; however, the authors paid particular attention to two specific sources of bias in the included studies related to the classification of the reference group – former drinker bias and occasional drinker bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported unadjusted summary relative risks of 1.09 (95% CI: 1.03 – 1.16, $I^2=10.66\%$) for low volume (1.30-<25g/day), 1.03 (95% CI: 0.93 – 1.14, $I^2=1.00\%$) for medium volume (25– < 45 g/day), 1.13 (95% CI: 0.98 – 1.30, $I^2=13.38\%$) for high (45– < 65 g/day) and 1.15 (95% CI: 1.01 – 1.13, $I^2=19.94\%$) for higher volume (65+ g/day) consumption compared with abstainers. The authors then undertook multivariate meta-regression in which estimates were adjusted for former and occasional drinker biases, geographic location of the study and whether the study had controlled for smoking status. The fully adjusted relative risks are 1.08 (95% CI: 1.04 – 1.11) for low volume, 1.07 (95% CI: 1.02 – 1.12) for medium volume, 1.14 (95% CI: 1.08 – 1.22) for high and 1.18 (95% CI: 1.10 – 1.27) for higher volume consumption. In stratified analysis, studies without occasional or former drinker biases had the highest effect sizes; for low (n=6) the relative risk was 1.23 (95% CI: 1.05 – 1.45) and for medium-high (n=3) the relative risk was 1.20 (95% CI: 1.00 – 1.43). Summary of findings is presented in Figure 53.

The included review reported a statistically significant association across all categories of alcohol consumption only in adjusted analyses. This type of analysis was not undertaken by the other systematic identified at full text. The findings across the studies are consistent in that they all either report a non-significant finding or a small statistically significant positive association. The WCRF¹⁵⁸ reported a non-significant summary RR for an increase of one alcoholic drink per day of 1.01 (95% CI: 0.99-1.02; $I^2=34.4\%$; heterogeneity=0.06; n=25). In contrast, Bagnardi 2015¹², which included 43 studies, reported a statistically significant effect for low (≤ 12.5 g/day) (RR = 1.04 (95% CI: 1.01–1.08, $I^2=0\%$) and moderate (≤ 50 g/day) RR = 1.06 (95% CI: 1.01–1.11, $I^2=17\%$) consumption but not for heavy drinking (>50 g/day) 1.09 (95% CI: 0.98–1.21, $I^2=37\%$). These estimates were similar to those reported by the same group in an earlier study¹¹⁴.

Figure 53 Summary of findings: Prostate

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Prostate cancer	1 SR ¹⁷⁶ (16 prospective cohorts, 1 retrospective cohort, 5 hospital-based case-control and 5 population-based case-control studies, n=49,848 cases)	1 SR, including 16 prospective cohorts, 1 retrospective cohort, 5 hospital-based case-control and 5 population-based case-control studies with unknown risk of bias, reported unadjusted summary RR of 1.09 (95% CI: 1.03 – 1.16, I ² =10.66%) for low volume (95% CI: 1.30- <25g/day), 1.03 (0.93 – 1.14, I ² =1.00%) for medium volume (25– < 45 g/day), 1.13 (95% CI: 0.98 – 1.30, I ² =13.38%) for high (45– < 65 g/day) and 1.15 (95% CI: 1.01 – 1.13, I ² =19.94%) for higher volume (65+ g/day) consumption compared with abstainers. Fully adjusted summary RRs were 1.08 (95% CI: 1.04 – 1.11) for low volume, 1.07 (95% CI: 1.02 – 1.12) for medium volume, 1.14 (95% CI: 1.08 – 1.22) for high and 1.18 (95% CI: 1.10 – 1.27) for higher volume consumption compared with abstainers. P number for dose-response analysis not reported in the systematic review.	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Prostate cancer **Risk of bias:** No formal quality assessment undertaken and both cohort and case-control studies included, less than 25% of participants from case-control studies **Inconsistency:** the statistical significance of the effect changes between the adjusted and unadjusted estimates. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil.

Abbreviations: SR = systematic review, RR = relative risk, g = grams

Stomach

Evidence from 20 prospective cohorts, 1 case-cohort and 2 nested case-control studies, (n cases=11,926) report a dose-response association between chronic alcohol consumption and stomach cancer. This association indicates that at 45g per day and above of alcohol consumption, there is an increased risk of risk of stomach cancer.

This is consistent with the conclusions of the other 4 systematic reviews that met the minimum criteria specified in the protocol, which report that higher levels of alcohol consumption confer an increased risk of stomach cancer.

Five systematic reviews^{12, 36, 132, 133, 162} were identified at full text on the association between alcohol consumption and stomach cancer. The systematic review by WCRF 2015b¹⁶², as part of its continuous update project, was selected for inclusion in the overview because it had the second most recent search date and met four of the six pre-specified inclusion criteria. It

partially met the remaining two criteria (comprehensive literature search and quality assessment) and in both cases justified its approach.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11) and included 20 prospective cohorts, one case-cohort, and two nested case-control studies. Risk of bias of the included studies was not assessed; however the authors restricted their review to cohort studies and nested case-control studies which are at lower risk of bias compared to case-control studies and discussed the quality of the included studies in their review. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a relative risk of 1.02 (95% CI: 1.00-1.04, $I^2=38.6\%$, $p=0.03$) per 10g ethanol/day. Similar results were obtained for gastric cardia and non-cardia cancers. Non-linear analysis showed that the dose-response association was significant at higher levels of alcohol intake (from 45 grams per day).

This is consistent with the conclusions of the remaining four systematic reviews that were identified at full text, three of which were from the same research group. Bagnardi¹² reported a pooled relative risk of 0.99 (95% CI: 0.92–1.06, $I^2=55\%$) for low (≤ 12.5 g/day), 0.97 (95% CI: 0.90–1.04, $I^2=46\%$) for moderate (≤ 50 g/day) and 1.21 (95% CI: 1.07–1.36, $I^2=41\%$) for heavy drinking (>50 g/day; 39 studies).

Figure 54 Summary of findings: Stomach

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Stomach cancer	1 SR ¹⁶² (20 prospective cohorts, 1 case-cohort and 2 nested case-control studies, n=11,926 cases)	1 SR, including 20 prospective cohorts, 1 case-cohort and 2 nested case-control studies with unknown risk of bias, reported a relative risk of 1.02 (95% CI: 1.00-1.04, $I^2=38.6\%$, $p=0.03$) per 10g ethanol increase per day. The dose-response association was significant at higher levels of alcohol intake (from 45 grams per day).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Stomach cancer **Risk of bias:** Studies were mostly large prospective cohorts studies which are at lower risk of bias than other observational study designs, however due to lack of explicit risk of bias assessment, this was downgraded by 1. **Inconsistency:** heterogeneity detected and explored but unable to be explained. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Detected.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval

Thyroid

Evidence from 7 cohorts and 17 case-control studies (n cases=9,990), report an association between chronic low levels of alcohol consumption and thyroid cancer, compared with non-drinkers. This association indicates that at low levels of alcohol consumption there is a decreased risk of thyroid cancer. Insufficient evidence is available to make any judgment at higher levels of consumption.

This is consistent with the conclusions of the other 3 systematic reviews that met the minimum criteria specified in the protocol, which reported a decreased risk or no difference in risk of thyroid cancer for low levels of alcohol consumption.

Four systematic reviews^{12, 31, 137, 145} were identified at full text on the association between alcohol consumption and thyroid cancer. The systematic review by Wang 2016a¹⁴⁵ was selected for inclusion in the overview because it had the most recent search date and met or partially met all of the pre-specified inclusion criteria.

The systematic review was of moderate quality (AMSTAR rating 6 out of 11) and included seven cohorts and 17 case-control studies. The risk of bias of the included studies was assessed using the NOS and ranged from 5 to 9 (median 8); overall the studies are considered to be at moderate risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported a summary relative risk of 0.81 (95% CI: 0.70-0.93, I²=59.7%) for low consumption (≤1 drink/day) and 0.71 (95% CI: 0.63-0.79, I²=0%) for moderate consumption (>1 drink/day) compared with non-drinkers. Insufficient data was available for higher levels of consumption. Summary of findings is presented in Figure 55.

This is consistent with the conclusions of the remaining 3 systematic reviews that were identified at full text all of which reported either inverse or null effects. Bagnardi¹² reported a pooled relative risk of 0.81 (95% CI: 0.74–0.88, I²=0%) for low (≤12.5 g/day) and 0.81 (95% CI: 0.71–0.94, I²=37%) for moderate (≤50 g/day) consumption. No estimate was able to be calculated for heavy drinking (>50g/day) (9 studies).

Figure 55 Summary of findings: Thyroid

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Thyroid cancer	1 SR ¹⁴⁵ (7 cohorts, 17 case-control studies, n=9,990 cases)	1 SR, including 7 cohort and 17 case-control studies with moderate risk of bias, reported a summary RR of 0.81 (95% CI: 0.70-0.93, I ² =59.7%) for low consumption (≤1 drink/day) and 0.71 (95% CI: 0.63-0.79, I ² =0%) for moderate consumption (>1 drink/day) compared with non-drinkers (p linearity = 0.112).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Thyroid cancer **Risk of bias:** Moderate risk of bias in included studies and evidence that study quality influences size of the effect. Less than 25% of the participants from case-control studies. **Inconsistency:** heterogeneity detected and not explained in sensitivity analysis. **Indirectness:** Nil. **Imprecision:** confidence intervals lack precision. **Publication bias:** Nil.

Abbreviations: SR = systematic review, RR = relative risk, CI = confidence interval.

Hip fracture

Evidence from 8 cohort and 5 case-control studies (n cases=4,293), report an association between chronic alcohol consumption and hip fracture, when compared with abstainers. This association indicates that at 0.5 to 1 drinks per day there is a decreased risk of hip fracture, but an increased risk at 2 or more drinks per day.

Five systematic reviews^{18, 34, 48, 89, 148} were identified at full text on the association between alcohol consumption and hip fracture/osteoporosis/low bone mass density (BMD). The systematic review by Berg 2008¹⁸ was selected for inclusion in the overview because it was the only one that met the minimum criteria set in the protocol. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of moderate quality (AMSTAR rating 7 out of 11), included 8 cohort and 5 case-control studies with a moderate overall risk of bias, and reported that for 0.5 to 1 drinks per day, the risk of hip fracture risk decreased. However, at >2 drinks the risk increased, when compared to abstainers. Summary of findings is presented in Figure 56.

The systematic review reported that the included studies adjusted for different potential confounders, but the majority did not adjust for all the identified important confounders: age, body mass index, smoking, dietary calcium, physical activity, and estrogen exposure in women. It also noted that most of the included studies reference groups included both lifetime abstainers and former drinkers.

Figure 56 Summary of findings: Hip fracture

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Hip fracture	1 SR ¹⁸ (8 cohort, 5 case-control, n cases=4,293)	One SR, including 8 cohort and 5 case-control studies with a moderate overall risk of bias reported that for 0.5 to 1 drinks per day, the risk of hip fracture risk decreased; however, at >2 drinks the risk increased, when compared to abstainers. Results from the categorical random effects meta-analysis reported that for 0 to 0.5 drinks/day RR=0.84 (95% CI: 0.70-1.01), 0.5 to 1.0 drinks/day RR=0.80 (95% CI: 0.71-0.91), >1 to 2 drinks RR=0.91 (95% CI: 0.76-1.09), >2 drinks RR=1.39 (95% CI: 1.08 – 1.79).	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Osteoporosis *Risk of bias:* Excluded studies that were rated as 'poor' quality from the meta-analysis. Included studies were rated 'fair' and did not account for all identified potential confounders and included case-control studies. Less than 25% of participants from case-control studies. **Inconsistency:** Nil. No heterogeneity detected. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil.

Abbreviations: SR = systematic review RR=relative risk, odds ratio and hazards ratios; CI = confidence interval

Gout

Evidence from 6 case-control and 6 cohort (n cases=42,924), report an association between chronic alcohol consumption and risk of gout, when compared to non/occasional drinkers. This association indicates that higher levels of alcohol consumption confer a large increased risk of risk of gout.

Two systematic reviews^{123, 144} were identified at full text on the association between alcohol consumption and gout. One systematic review by Wang 2013¹⁴⁴ met the minimum criteria set in the protocol. The systematic review was of moderate quality (AMSTAR rating 5 out of 11) and included 12 cohort and 5 case-control studies with an unclear risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported that alcohol consumption was associated with an increased risk of gout, with higher amounts of alcohol consumption associated with a greater risk of gout. Summary of findings is presented in Figure 57.

The risk of bias is unknown as no formal risk of bias assessment of included studies was conducted. Significant heterogeneity was detected, for low alcohol consumption (≤ 12.5 g/day) ($I^2=77.7\%$), and moderate heterogeneity was detected for moderate alcohol consumption (12.6-37.4g/day) ($I^2=45.1\%$) and for heavy drinking (≥ 37.5 g/day) ($I^2=67\%$) compared with non/occasional drinking. Subgroup analysis was conducted for cohort and case-control studies, and East Asian and Caucasian populations. These analyses had similar levels of heterogeneity. An analysis was also conducted where the study with the most excessive influence was removed for moderate (RR=1.72 (95% CI: 1.49-1.98), $I^2=46.2\%$) and high (RR=2.91 (95% CI: 2.61-3.26), $I^2=25\%$) intakes. The results of these were similar to those from the meta-analysis for both groups and heterogeneity remained similar for moderate intake; however, heterogeneity was substantially lower for the high group.

A dose response gradient was reported, showing that increased levels of alcohol consumption resulted in an increased risk of gout.

The reference group included none and occasional drinking, but occasional drinking was not defined. Results were included from both adjusted analyses and matched populations. The variables adjusted for varied between studies.

Figure 57 Summary of findings: Gout

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Gout	1 SR ¹⁴⁴ (6 Case-control, 6 Cohort, n cases=42,924)	One systematic review of unknown risk of bias reported an increased risk of gout with alcohol consumption compared to non/occasional drinking. Random effects meta-analysis reported a pooled RR for low (≤ 12.5 g/day) drinking of 1.16 (95% CI: 1.07-1.25), for moderate (12.6-37.4g/day) drinking RR=1.58 (95% CI: 1.50-1.66) (fixed effects) and for heavy drinking (≥ 37.5 g/day) RR=2.64 (95% CI: 2.26-3.09) compared with non/occasional drinking.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Gout *Risk of bias:* Included studies at unknown risk of bias. More than 25% of participants came from case-control studies. *Inconsistency:* Moderate heterogeneity was detected for heavy ($I^2=67.0\%$) and moderate ($I^2=45.1\%$). Considerable heterogeneity was detected for low drinking ($I^2=77.7\%$). *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* None detected.

Abbreviations: n = number of participants; SR = systematic review; CI = confidence interval, RR = relative risk.

Respiratory diseases

Pneumonia

Evidence from 2 cohort and 3 case-control (n cases=2371), report a dose-response association between chronic alcohol consumption and risk of pneumonia, when compared to non-drinkers. This association indicates that at 40g per day and above of alcohol consumption, there is an increased risk of risk of pneumonia.

One systematic review by Samokhvalov 2010b¹¹⁷ was identified at full text on the association between alcohol consumption and pneumonia morbidity or mortality. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of moderate quality (AMSTAR rating 6 out of 11) and included 2 cohort and 3 case-control studies with an unclear risk of bias. It reported a dose-response relationship between alcohol consumption and risk of community-acquired pneumonia (CAP) (RR=1.06 (95% CI: 1.01–1.11) per standard drink (12g pure alcohol) per day). This effect size is quite precise and includes a large number of participants including a cohort study with 104,491 participants. The systematic review also reported an increased risk of CAP in those with alcohol use disorder (AUD) compared to people without AUD (RR = 8.22 (95% CI: 4.85–13.95)). Summary of findings is presented in Figure 58.

Figure 58 Summary of findings: Pneumonia

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Pneumonia (morbidity and/or mortality)	1 SR ¹¹⁷ (2 Cohort (n=108,658), 3 Case-control (n=3,442), n cases=2371))	One systematic review with an unknown risk of bias found an increased risk of CAP morbidity or mortality of RR=1.06 (95% CI 1.01–1.11) per standard drink (12g pure alcohol) per day compared with non-drinkers. For those with AUD compared to people without AUD the risk was RR=8.22, (95% CI 4.85–13.95). P number for dose-response analysis not reported in the systematic review.	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕⊕○○

GRADE reasons for downgrading or upgrading:

Pneumonia **Risk of bias:** Included studies at unknown risk of bias. Less than 25% of participants from case-control studies. **Inconsistency:** Nil. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** None detected.

Abbreviations: AUD = alcohol use disorders; n = number of participants; SR = systematic review; RR = relative risk CI = confidence interval; CAP = community-acquired pneumonia

Tuberculosis

Evidence from 18 case-control and 3 cohort studies (n cases=4,305), report an association between chronic alcohol consumption and tuberculosis, when compared with non-drinkers. This association indicates that at 40g per day and above of alcohol consumption, there is an increased risk of risk of tuberculosis. The results should be interpreted with caution due to the population not being representative of the general population.

Two systematic reviews^{70, 100} were identified at full text on the association between alcohol consumption and tuberculosis. The systematic review by Lonnroth 2008⁷⁰ was selected for inclusion in the overview because it was the only systematic review identified that met the minimum criteria set in the protocol. The systematic review was of moderate quality (AMSTAR rating 5 out of 11) and included 3 cohort and 18 case-control studies with an unclear risk of bias. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported that alcohol consumption >40g per day may be associated with an increased risk of tuberculosis. Summary of findings is presented in Figure 59.

The risk of bias is unknown as no formal risk of bias assessment of included studies was conducted. However, the systematic review noted that the included studies may be at a higher risk of bias due to residual confounding from different methods of adjustment of socioeconomic variables. The outcome was also downgraded for serious indirectness as the populations in the included studies are not representative of the general population, for example, coming from prison or social services populations. The systematic review notes that these populations may have higher levels of alcohol consumption than the general population.

Significant heterogeneity ($I^2=82\%$) was reported in the initial analysis of high levels of alcohol consumption (>40g per day). However, sensitivity analysis was conducted and when the 3 smallest studies and the studies with the largest and lowest effect sizes were excluded from the analysis heterogeneity was low ($I^2=15\%$). This analysis reported that high levels of alcohol consumption (>40g per day) is associated with an increased risk of tuberculosis (OR = 2.96 (95%CI: 2.28–3.85)). At levels <40g per day OR = 1.08 (95% CI: 0.82–1.40) (4 studies, $I^2=0$).

Figure 59 Summary of findings: Tuberculosis

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Tuberculosis	1 SR ⁷⁰ (18 Case-control, (cases=4,305, controls=4,684), 3 Cohort (n=60,624))	One systematic review including 18 case-control and 3 cohort studies with an unknown risk of bias examined the association between alcohol consumption and tuberculosis. Eleven studies were included in the analysis of high levels of alcohol consumption (>40g) per day and tuberculosis (OR = 3.50 (95% CI: 2.01–5.93)), but with significant heterogeneity ($I^2=82\%$). When the 3 smallest studies and the studies with the largest and lowest effect sizes were excluded from the analysis OR = 2.96 (2.28–3.85) ($I^2=15\%$) Four studies were included in the low exposure category (<40g per day) and reported OR = 1.08, (95% CI: 0.82–1.40).	Risk of bias: -2 Inconsistency: 0 Indirectness: -2 Imprecision: 0 Publication bias: -1	⊕○○○

GRADE reasons for downgrading or upgrading:

Tuberculosis **Risk of bias:** Included studies at unknown risk of bias. There may be residual confounding due to different methods of adjustment of socioeconomic variables. Less than 25% of participants from case-control studies. The comparator varied across the included studies. **Inconsistency:** Significant heterogeneity ($I^2=82\%$) was reported in the initial analysis of high levels of alcohol consumption but was investigated through sensitivity analysis. **Indirectness:** Very serious indirectness for the population. The systematic reviews notes that participants in included studies are recruited from groups such as prisoners and social service clients that are likely to have higher alcohol intake levels than the general population. **Imprecision:** Nil. **Publication bias:** Suspected.

Abbreviations: n = number of participants; SR = systematic review; CI = confidence interval

Seizures (co-morbidity)

Evidence from 6 case-control studies (n cases=934), report a dose-response association between chronic alcohol consumption and seizures, when compared with non-drinkers. The results should be interpreted with caution due to different outcome definitions and limited evidence.

Two systematic reviews^{115, 141} were identified at full text on the association between alcohol consumption and seizures (co-morbidity). One systematic review by Samokhvalov 2010a¹¹⁵ met the minimum criteria set in the protocol. The quality of evidence across the underlying

primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 3 out of 11) and included 6 case-control studies with an unknown risk of bias. The systematic review reported a dose-response relationship between increased levels of alcohol consumption and increased risk of epilepsy/unprovoked seizures. The systematic review did not report whether confounders were adjusted for and, if so, which ones. It also had a very small number of cases and studies included and pooled together the outcomes of unprovoked seizures and epilepsy. Summary of findings is presented in Figure 60.

Figure 60 Summary of findings: Seizures (co-morbidity)

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Seizures (co-morbidity)	1 SR ¹¹⁵ (6 case-control (cases n=934, controls n=1,398))	One systematic review including 6 case-control studies with an unknown risk of bias examined the association between alcohol consumption and epilepsy/unprovoked seizures. The risk of epilepsy/unprovoked seizures for <50g daily average consumption of pure alcohol reported RR = 1.29 (95% CI: 1.03-1.61) compared with non-drinkers (4 studies). A dose-response analysis reported that consumption of 12, 48, 72, and 96g of alcohol per day 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 (p = 0.787).	Risk of bias: -2 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	⊕○○○

GRADE reasons for downgrading or upgrading:

Seizures (co-morbidity) **Risk of bias:** Unknown risk of bias. **Inconsistency:** No statistically heterogeneity detected however clinical heterogeneity is suspected due to inclusion of different outcome measures. **Indirectness:** indirectness for outcome due to definition being both unprovoked seizures and epilepsy. **Imprecision:** Moderate. Small sample sizes. **Publication bias:** None detected.
P numbers not provided

Abbreviations: n = number of participants; SR = systematic review; CI = confidence interval; RR = relative risk; g = grams

Dementia/cognitive impairment

Evidence from 15 prospective cohort studies (n cases=unclear), report an association between chronic alcohol consumption and risk of dementia/cognitive impairment, when compared with non-drinkers. This association indicates low to moderate alcohol consumption is associated with a decreased risk of dementia/cognitive impairment; however there is no difference in risk at higher levels of consumption.

The results of the other systematic review identified at full text that met the minimum criteria, reported that alcohol abstinence and heavy drinking resulted in an increased risk, compared to moderate consumption.

Thirteen systematic reviews^{9, 19, 22, 32, 33, 35, 63, 68, 82, 92, 95, 96, 125} were identified at full text on the association between alcohol consumption and dementia/cognitive impairment. The systematic review by Anstey 2009⁹ was selected for inclusion in the overview. One other systematic review⁶³ also met the minimum criteria; however, this had a more restrictive search.

The included systematic review⁹ was of poor quality (AMSTAR rating 3 out of 11) and included 15 prospective cohort studies with an unknown risk of bias. However, the included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies, which are susceptible to the introduction of fewer biases than case-control study designs. All included studies in the systematic review conducted multivariate analysis and adjusted for a minimum of age and sex; however, the other confounders adjusted for varied between studies. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review reported light to moderate alcohol consumption (ranges included 1-21, 1-27, 2-28, 1-14 grams per week or unspecified units per week) was associated with a lower risk of Alzheimer's disease, vascular dementia and any dementia compared to non-drinking (RR=0.72 (95% CI: 0.61-0.87); RR=0.75 (95% CI: 0.57-0.98); RR=0.74 (95% CI: 0.61-0.91), respectively). There was no difference reported for heavy alcohol consumption compared with non-drinking. Summary of findings is presented in Figure 61.

The systematic review also reported results on former drinkers compared with lifetime abstainers. Only 5 studies provided information on these two groups. Three of the identified studies reported no differences between former drinkers compared with lifetime abstainers for risk of dementia/cognitive decline. Another study reported that exclusion of former drinkers from the abstainer group resulted in a decreased effect size. The remaining study reported a 20%–60% increase in odds of dementia incident in former drinkers when compared to lifetime abstainers. The reference groups may include former drinkers in the non-drinking category and there were a limited number of studies reporting data on these groups, where this would have an effect on the results.

The results are consistent with the conclusion of the other systematic review identified at full text that met the minimum criteria, which reported that there was evidence of an association between alcohol abstinence and/or heavy drinking and increased risk of cognitive impairment⁶³.

Figure 61 Summary of findings: Dementia and cognitive decline

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Dementia and cognitive decline	1 SR ⁹ (15 prospective cohorts, n=unclear)	<p>One SR with an unknown risk of bias reported a decreased risk of dementia/cognitive impairment; however there is no difference in risk at higher levels of consumption.</p> <p>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).</p> <p>The meta-analysis comparing heavy alcohol consumption with not drinking reported no significant differences.</p>	<p>Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1</p>	⊕○○○

GRADE reasons for downgrading or upgrading:

Dementia and cognitive decline *Risk of bias:* Included studies at unknown risk of bias. *Inconsistency:* Significant heterogeneity was detected for light to moderate drinking compared to non-drinking for the outcome of Alzheimer's disease, and reasons for heterogeneity not explored. *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* Not assessed.

Abbreviations: SR = systematic review; RR = odds ratios, risk ratios and hazard ratios; CI = confidence interval

Question 3: Health risks and benefits for pregnant women

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?

Inconsistency of measurement of maternal alcohol consumption across primary studies and the methods used to quantify prenatal alcohol exposure limits the investigation of dose and response. This is of particular importance when considering fetal exposure where various methods of estimation of maternal alcohol consumption have been used in studies including average daily estimate of consumption, average consumption across pregnancy, and number of drinks per week. These methods are insensitive to the dose of alcohol consumed per occasion and the frequency of consumption that affect the intensity of fetal exposure, thereby masking the ability to estimate the risk to the fetus from maternal drinking at low, moderate and binge levels⁸⁶.

Figure 62 Systematic reviews identified at full text for question 3

Importance	Outcomes	Sub-outcomes	No of reviews (SRs) identified at full text*	No of reviews (SRs) included in overview
Critical	Developmental delay	Child neuropsychological	1	0
		Neurodevelopment outcomes	1	0
		Communication/language acquisition delay & development	1	1
	FASD	Gross motor deficits	2	1
	Small for gestational age	N/A	1	1
	Low birth weight	N/A	1	1
	Birth defects	Orofacial clefts	2	0
		Microtia	1	0
		Congenital heart defects	3	0
		Birth defects including FASD	1	0
		Neural tube defects	1	0
		Liver dysfunction	1	0
		Anorectal malformations	1	0
		Cryptorchidism	1	0
		Stillbirth	No systematic reviews identified	
Behavioural problem	Disruptive behaviour disorders	1	0	
	ADHD	1	0	
	Child behaviour	1	0	
Important but not critical	Neonatal withdrawal	No systematic reviews identified		
	Spontaneous abortion and miscarriage	No systematic reviews identified		
	Premature birth	N/A	1	1

*For full details of reasons for exclusion of systematic reviews please see Technical Report.

Preterm birth

Evidence from 12 cohort and 2 case-control studies (n cases=12,888), report a dose-response association between alcohol consumption during pregnancy and preterm birth, when compared with non-drinkers. This association indicates that at 19g per day and above of alcohol consumption, there is an increased risk of risk of preterm birth.

One systematic review⁹⁰ was identified at full text on the association between alcohol consumption and preterm birth. The systematic review by Patra 2011⁹⁰ was selected for inclusion in the overview because it was the only one identified for this outcome and met the minimum criteria for inclusion. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 4 out of 11) and included 2 case-control and 12 cohort studies with an unknown risk of bias. The systematic review reported a dose-response relationship between increasing levels of alcohol consumption >10g/day and increased risk of preterm birth. Summary of findings is presented in Figure 63.

The systematic review included studies with both unadjusted and adjusted analyses. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies. Subgroup analysis showed that the effect size observed was similar in studies that adjusted for smoking and when analysing each trimester separately. Studies that did not adjust for any confounders reported an increased risk at a much higher dose of alcohol intake than when analysing all studies (adjusted and unadjusted) together. Subgroup analysis showed a difference between study design types with the effect size observed being larger in case-control studies than in cohort studies.

Figure 63 Summary of findings: Preterm birth

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Preterm birth	1 SR ⁹⁰ (12 cohort, 2 case-control, n=280,443, n cases= 12,888)	One SR, including 12 cohort and 2 case-control studies reported a dose-response relationship between increased levels of alcohol consumption and increased risk of preterm birth. In a dose-response meta-analysis 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 (p nonlinearity < 0.001). Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	⊕○○○

GRADE reasons for downgrading or upgrading:

Preterm birth *Risk of bias:* The systematic review reports that studies were assessed using STROBE, but the results of the quality assessments are not provided. The number of participants in cohort and case-control studies is not reported. *Inconsistency:* Considerable heterogeneity detected ($I^2 = 89\%$). *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* Nil. *Dose response:* Detected.

Abbreviations: SR = systematic review; g = grams, n = number of participants; RR = relative risk; CI = confidence interval

Low birthweight

Evidence from 15 cohort and 4 case-control studies (n cases= 20,582), report a dose-response association between alcohol consumption during pregnancy and low birthweight, when compared with non-drinkers. This association indicates that at 10g per day and above of alcohol consumption, there is an increased risk of risk of low birthweight.

One systematic review⁹⁰ was identified at full text on the association between alcohol consumption and low birthweight. The systematic review by Patra 2011⁹⁰ was selected for inclusion in the overview because it was the only one identified for this outcome and met the minimum criteria for inclusion. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 4 out of 11) and included 4 case-control and 15 cohort studies with an unknown risk of bias. The systematic review reported a dose-response relationship between increasing levels of alcohol consumption >10g/day and increased risk of low birthweight, with a large effect size reported at higher levels of consumption (120 g/day RR = 7.48 (95% CI: 4.46–12.55)). Summary of findings is presented in Figure 64.

The systematic review did not restrict included studies to those with multivariate analysis. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies. Subgroup analysis showed that the dose response observed was similar in studies that adjusted for smoking and when analysing each trimester separately.

Figure 64 Summary of findings: Low birthweight

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Low birthweight	1 SR ⁹⁰ (15 cohort, 4 case-control, n=277,300, n cases=12,888)	One SR, including 15 cohort and 4 case-control studies with an unknown risk of bias, reported a dose-response relationship between increased levels of alcohol consumption and increased risk of low birthweight. In a dose-response meta-analysis 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 were associated with increased risk of low birthweight, with 120 g/day RR = 7.48 (95% CI: 4.46–12.55) (p nonlinearity < 0.001). Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1 Effect size: +1	⊕○○○

GRADE reasons for downgrading or upgrading:

Low birthweight *Risk of bias:* The systematic review reports that studies were assessed using STROBE, but the results of the quality assessments are not provided. The number of participants in cohort and case-control studies is not reported. *Inconsistency:* Considerable heterogeneity detected ($I^2 = 80\%$). *Indirectness:* Nil. *Imprecision:* Nil. *Publication bias:* Nil. *Dose response:* Detected. *Effect size:* Large at 120g/day.

Abbreviations: SR = systematic review; g = grams, n = number of participants; RR = relative risk; CI = confidence interval

Small for gestational age

Evidence from 2 cohort and 6 case-control studies (n cases=8679), report a dose-response association between alcohol consumption during pregnancy and small for gestational age, when compared with non-drinkers. This association indicates that at 10g per day and above of alcohol consumption, there is an increased risk of small for gestational age.

One systematic review⁹⁰ was identified at full text on the association between alcohol consumption and small for gestational age. The systematic review by Patra 2011⁹⁰ was selected for inclusion in the overview because it was the only one identified for this outcome and met the minimum criteria for inclusion. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 4 out of 11) and included 6 case-control and 2 cohort studies with an unknown risk of bias. The systematic review reported a dose-response relationship between increasing levels of alcohol consumption >10g/day and increased risk of small for gestational age. Summary of findings is presented in Figure 65. Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.

The systematic review did not restrict included studies to those with multivariate analysis and included studies with both unadjusted and adjusted analyses. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies but all studies adjusted for smoking. Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.

Figure 65 Summary of findings: Small for gestational age

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Small for gestational age	1 SR ⁹⁰ (2 cohort, 6 case-control, n=136,949, n cases=8679)	1 SR, including 2 cohort and 6 case-control studies with an unknown risk of bias, reported a dose-response relationship between increased levels of alcohol consumption and increased risk of SGA. In a dose-response meta-analysis 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 (p nonlinearity < 0.001). At 7 drinks (at US conversion of 12g per drink) per day the RR = 2.02 (1.47-2.77). Subgroup analysis showed that the dose response observed was similar when analysing each trimester separately.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	⊕○○○

GRADE reasons for downgrading or upgrading:

Small for gestational age **Risk of bias:** The systematic review reports that studies were assessed using STROBE, but the results of the quality assessments are not provided. The number of participants in cohort and case-control studies is not reported. **Inconsistency:** Considerable heterogeneity detected ($I^2 = 92\%$). **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Nil. **Dose response:** Detected, therefore upgraded by 1.

Abbreviations: SR = systematic review; SGA = small for gestational age;

Child motor function

Evidence from 23 studies (n case-control or cohort=unclear; n case=unclear), report an association between alcohol consumption during pregnancy and child motor function, when compared with non-drinkers. This association indicates low levels of alcohol consumption may confer no increased risk, however higher levels may confer an increased risk of poorer child motor function. The results should be interpreted with caution due to different scales to measure child motor function.

One systematic review¹⁶ was identified at full text on the association between alcohol consumption and child motor function. The systematic review by Bay 2011¹⁶ was selected

for inclusion in the overview as it was the only one identified for this outcome and met the minimum criteria for inclusion. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

The systematic review was of poor quality (AMSTAR rating 4 out of 11) and included 23 studies (for the exposure levels extracted for this overview). The systematic review reported that for low-moderate alcohol intake (1–7 drinks/week, at less than one drink per day) there was no difference but at moderate-high daily intake (3–5 drinks/day) and low daily alcohol consumption (1–2 drinks/day, at levels from 10 drinks/week) there was an increased effect on child motor development. Summary of findings is presented in Figure 66. The systematic review did not restrict included studies to those with multivariate analysis and included studies with both unadjusted and adjusted analyses. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies.

The systematic review did not restrict included studies to those with multivariate analysis and included studies with both unadjusted and adjusted analyses. Of those studies that had adjusted analyses, the confounders adjusted for varied between studies.

Figure 66 Summary of findings: Child motor function

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Child motor function ¹⁵	1 SR ¹⁶ (23 studies for low, low-moderate and moderate-high intakes (number case-control or cohort unknown) n=unknown)	1 SR, including 23 studies investigated the effects of low, low-moderate and moderate-high alcohol intakes during pregnancy and child motor function. 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 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	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1	⊕○○○

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
		<p>compared to not drinking during pregnancy.</p> <p>Seven out of 13 studies on low daily alcohol consumption (1–2 drinks/day) reported significant effects on child motor development at maternal alcohol consumption > 10 drinks/week when compared to not drinking (6 studies) or < 0.1oz/day alcohol consumption (1 study) during pregnancy.</p> <p>Six out of 13 studies reported an increased risk for low daily alcohol consumption (1–2 drinks/day, at levels from 10 drinks/week) on fine motor functions compared to not drinking (5 studies) or < 0.1oz/day alcohol consumption (1 study) during pregnancy.</p> <p>Four out of 13 studies on low alcohol consumption (1–2 drinks/day, at levels from 10 drinks/week) reported poorer performances of gross motor skills compared to not drinking (3 studies) or < 0.1oz/day alcohol consumption (1 study) during pregnancy.</p> <p>For low-moderate exposure (1–7 drinks/week, at less than one drink per day) there was no difference reported on child motor development.</p> <p>The studies all used different scales to measure child motor function.</p>		

GRADE reasons for downgrading or upgrading:

Child motor function *Risk of bias:* The systematic review reports that the included studies were generally of high quality on NOS, however the score of each of the individual studies was not provided. There may be a greater risk of bias due to the inclusion of case-control study designs. **Inconsistency:** Significant heterogeneity detected that precluded meta-analyses. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Not assessed but the systematic review mentions that the included studies may be affected by publication bias.

Abbreviations: SR = systematic review; n = number of participants;

Communication

Communication Delay

Evidence from 1 retrospective cohort study (n= 1,739), reports no association between alcohol consumption during pregnancy and communication delay in children, when compared with non-drinkers.

Communication Development

Evidence from 1 retrospective cohort study and 1 prospective cohort study (n= 14,035), reports no association between alcohol consumption during pregnancy and communication development in children, when compared with non-drinkers.

Both of these outcomes derive from the one systematic review⁸⁵. The systematic review included studies that explored language acquisition and development in children using different validated instruments. Each instrument covered different domains or aspects of language development at different ages and in different populations. This is why this outcome has been presented as communication delay and development and not amalgamated.

Communication Delay

One systematic review was retrieved from the search strategy and public submission process⁸⁵, and assessed the association between gestational alcohol and communication delays in children. The quality of evidence across the underlying primary studies included in the systematic review was assessed as moderate quality in GRADE.

The review assessed the specific outcome of communication delays (using the Communication scale from Ages and Stages Questionnaire) when children were 2 years of age. The data on this outcome derived from one study involving 1,739 women and their children based in Western Australia. Alcohol exposure was categorised into two groups: low exposure (20 g or less per occasion less than weekly or less than daily) and abstainers. The study adjusted for common confounders such as maternal age, parity, smoking for each trimester, family factors, amongst many others.

This systematic review was judged to be at moderate quality (AMSTAR rating 7 out of 11). The review authors comprehensively assessed all potential risk of biases in this retrospective cohort study. Overall, for low drinkers in the first trimester, the odds of language delay were 0.97 (95% CI 0.65 to 1.43). For low drinkers in the second trimester, the odds of language delay were 0.87 (95% CI 0.57 to 1.23) and similarly, there was slightly reduced odds of language delay in the third trimester (OR 0.84, 95% CI 0.57 to 1.23). None of the results were statistically significant. The Summary of findings is presented in Table 2. There were no serious concerns with the conduct or reporting of this outcome and therefore the evidence was judged to be moderate quality.

Communication Development

The same systematic review⁸⁵ also assessed communication development in children. The quality of evidence across the underlying primary studies included in the systematic review was assessed as very low quality in GRADE.

Two cohort (one retrospective; the other prospective) studies reported on this outcome and used two different tools to measure the outcome. Children were assessed using either a 7-item language measure of the Denver Development Scale or the Sequenced Inventory of Communication Development scale, and at either one, two or three years of age. In total, 14,035 women and their children were involved in these two studies based in the USA. Alcohol exposure was defined either as mean alcoholic drinks per day during pregnancy or absolute alcohol per day. One study did not adjust for confounders while the other study assessed common confounders such as maternal age, parental education, ratings of psychosocial stress amongst other factors.

As previously mentioned under Communication Delay, this systematic review was judged to be at moderate quality (AMSTAR rating 7 out of 11). Based on results of the retrospective cohort study (using the 7-item scale), there did not appear to be any dose-response relationship between lower levels of language development and mean number of drinkers per day however covariates were not adjusted for in this study. Similarly, results from the prospective study (using the Sequenced Inventory Developmental Scale) indicated that there were no significant differences in language development at 1, 2 or 3 years on all three alcohol measures (including abstinence, 1/3 of a UK standard drink per day, or > 1/3 to 1.5 UK standard drinks per day). The Summary of findings is presented in Table 2. The systematic review assessed risk of bias to be at moderate or high level overall for both studies and therefore we downgraded the evidence by two points.

Figure 67 Summary of findings: Communication Delay and Development

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
Communication (language) delay	One SR ⁸⁵ (1 retrospective cohort study, n= 1,739)	One SR, including 1 retrospective cohort study reported overall, for low drinkers in the first trimester, the odds of language delay were 0.97 (95% CI 0.65 to 1.43). For low drinkers in the second trimester, the odds of language delay were 0.87 (95% CI 0.57 to 1.23) and similarly, there was slightly reduced odds of language delay in the third trimester (OR 0.84, 95% CI 0.57 to 1.23). None of the results were statistically significant.	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕⊕⊕○
Communication development	One SR ⁸⁵ , (1 retrospective cohort study and 1 prospective cohort study, n= 14,035)	One SR, including 1 retrospective cohort study and 1 prospective cohort study reported no significant differences in language development. Based on results of the retrospective cohort study (using the 7-item scale), there did not appear to be any dose-response relationship between lower levels of language development and mean number of drinkers per day however covariates were not adjusted for in this study. Similarly, results from the prospective study (using the Sequenced Inventory Developmental Scale) indicated that there were no significant	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕○○○

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	Quality of evidence
		differences in language development at 1, 2 or 3 years on all three alcohol measures (including abstinence, 1/3 of a UK standard drink per day, or > 1/3 to 1.5 UK standard drinks per day).		

GRADE reasons for downgrading or upgrading:

Communication (language) delay **Risk of bias:** None. Author's classified the included study as at minimal risk of bias. **Inconsistency:** Not applicable. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Not applicable.

Communication development **Risk of bias:** Author's classified one included study as moderate and the other as high risk of bias. **Inconsistency:** Detected but results were reported separately. **Indirectness:** Nil. **Imprecision:** Nil. **Publication bias:** Not assessed but only included 2 studies.

Abbreviations: SR = systematic review; RR = relative risk; OR = odds ratio; CI = confidence interval

Question 4: Health risks and benefits for breastfeeding women

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?

No systematic reviews were identified at full text for question 4.

Mendelian randomisation

The literature search retrieved a number of genome-association (also referred to as Mendelian randomisation) studies and these studies have been reported separately as they did not conform to the pre-specified selection criteria of the overview. The aim of these studies was to use the genetic variance in the alcohol dehydrogenase (ADH1B) or aldehyde dehydrogenase (ALDH2) gene as a surrogate for alcohol exposure to provide evidence of a causal link between alcohol exposure and risk of cancer, cardiovascular disease and alcohol-related diseases (such as cirrhosis) which is less likely to be subject to unmeasured confounding.

As this is a rapidly emerging field, it is important to take note of these types of studies identified through the literature search. At this stage, without having conducted a formal assessment of the studies, a brief description and summary of the main findings of these studies have been provided in the Technical Report.

International Agency for Research on Cancer (IARC) report

IARC published its most recent monograph on Alcohol Consumption and Ethyl Carbamate in 2010⁵⁰ and a monograph on Personal Habits and Indoor Combustion in 2012 which also considered alcohol consumption⁵¹. The monographs were not considered for inclusion in the overview as the methodology underpinning them is not reported in sufficient detail. Although IARC undertakes systematic reviews, the details of these are not publically available and the monographs are a reflection of the views of the expert working group based on their appraisal of the underlying reviews. Nevertheless, as a global authority on carcinogenicity, the IARC monograph should reasonably be compared with the findings of the overview with respect to cancer.

IARC 2012⁵¹ concluded that there is sufficient evidence in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas. For cancer of the kidney and non-Hodgkin lymphoma, there is evidence suggesting lack of carcinogenicity.

These conclusions are similar to those of WCRF¹⁵¹⁻¹⁶², which informed a substantial number of cancer outcomes in the overview, with minor differences presented in the table below.

Figure 68 Evidence from WCRF/AICR and IARC

	WCRF/AICR	IARC (2012)
Convincing	Mouth, pharynx and larynx Oesophagus (squamous cell) Colorectum (men) Liver Breast (pre and post-menopausal)	Oral cavity Pharynx Larynx Oesophagus Colorectum Liver (hepatocellular carcinoma) Female breast
Probable*	Colorectum (women) Stomach Kidney (decreases risk)	Pancreas
Limited – suggestive*	Pancreas	
Substantial effect on risk unlikely		Kidney Non-Hodgkin Lymphoma

* These categories are not used by IARC

Discussion

Summary of main results

38 systematic reviews (for 53 outcomes) were included in the overview. 5 outcomes were reported for the short term health risks and benefits of alcohol consumption associated with any single episode of drinking. 42 outcomes were reported for the long term health risks and benefits associated with alcohol consumption. 6 outcomes were reported for the health risks and benefits of alcohol consumption for pregnant women and their fetuses, babies and children. No systematic reviews were identified for the health risks and benefits alcohol consumption for breastfeeding women and their babies.

Overall, the quality of evidence across all outcomes was very low, predominately due the observational nature of the included studies and limitations in reporting and concerns about the conduct of both the systematic reviews and primary studies, which led to low ratings on the GRADE and AMSTAR scales. Six outcomes were rated as low and three were rated as moderate.

Quality of the evidence

An overview of systematic reviews is dependent on the quality of the included systematic reviews. No additional information was sought by contacting review authors or consulting the primary studies. The quality of the included systematic reviews ranged from 2 to 9 (out of 11) on the AMSTAR checklist, although it should be noted that the AMSTAR checklist itself may not accurately reflect the quality of the included studies. Not all included reviews assessed the risk of bias in the primary studies. In those which did assess risk of bias, the assessments were often poorly reported and insufficient for reliable interpretation of the review and its included studies. 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. 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 studies did not meet all the criteria set in the protocol and only met the minimum criteria (2 out of criteria 1-4).

One area of relative strength was the evidence on the association between alcohol consumption and cancer risk. The work of the WCRF and its continuous update project, although rating 7 out of 11 on the AMSTAR checklist, was considered methodologically sound, rigorous, and high quality. Other reviews also only scored 7 out of 11 on the AMSTAR checklist, but considered factors like study design type and recall biases within the included studies, such as Zeisser 2013¹⁷¹ and Stockwell 2016¹²⁶. There were some reviews that scored up to 9 out of 11 on the AMSTAR checklist so were considered of higher quality.

Overall, the quality of evidence across all outcomes was very low predominantly due to the poor quality or lack of quality assessment of the included studies, which lead to a high risk of bias; inconsistency, due to high levels of heterogeneity detected and the risk of publication bias. As most of the systematic reviews identified were of poor quality, the GRADE outcome is lower than would be expected.

The application of GRADE to a public health context, such as examining the health effects of exposure to alcohol, has limitations when the evidence is largely observational in nature. Given that randomised controlled trials are not often ethically appropriate or feasible to examine this exposure, observational data studies usually provide the best available evidence. Similarly, using GRADE to assess the quality of systematic reviews in overviews is a developing methodology and presents further challenges, particularly as the systematic reviews identified in this evidence evaluation often did not contain sufficient information about the included primary studies.

As such the quality of evidence examining the health effects of alcohol consumption across most outcomes was assessed as being very low in GRADE, with some outcomes assessed as having a low or moderate quality rating. This is mainly due to the issues raised above and poor reporting of key aspects of the included studies and also concerns about conduct, including the assessment of the risk of bias of the included primary studies, consideration of confounding factors, exploration of possible causes of heterogeneity, and the risk of publication bias. For further information on methods and limitations refer to the technical report.

Potential biases and limitations

For the studies that reported a J-shaped association there was discussion in some systematic reviews around the reference categories and the potential for abstainer bias, such as in Stockwell 2016¹²⁶. This is because the reference group in the included studies can vary between studies. The reference groups may consist of occasional drinkers, lifetime abstainers or current abstainers, which may include former drinkers. The systematic reviews often variously define these groups and each of these groups may carry differing levels of excess risk. For example, if the reference group includes former drinkers who may still carry with them the risk incurred from prior drinking, then this may result in an under-estimation of the actual risk. Some systematic reviews, for example the review on all-cause mortality, do explore the impact of different reference groups on the result.

Another important consideration is how alcohol consumption was measured. This could be by frequency and/or dose and these could be quantified by grams alcohol consumed or drinks consumed. Note that the amount of alcohol per standard drink differs across countries. In addition, measurement could be prospective or retrospective, and participants could be asked about consumption patterns or absolute amounts over differing periods of time. This inconsistency of measurement across primary studies and the methods used to combine exposures may produce unreliable results. This is of particular importance when considering fetal exposure where various methods of estimation of alcohol consumption are used in studies including average daily estimate of consumption, average consumption across pregnancy, and number of drinks per week. These methods are insensitive to the dose of alcohol consumed per occasion and the frequency of consumption that affect the intensity of fetal exposure⁸⁶.

A potential bias is that many of the included studies in the systematic reviews did not adjust for potential confounding variables, and when they did, the number of variables included in the analysis varied widely from age and sex only to fully adjusted models. Consequently, this reduces the confidence of these results as there may be residual confounding present.

Many of the systematic reviews 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 biases than prospective cohort study designs, our confidence in the results is decreased. Additionally, some systematic reviews did report study types separately and found differences in the observed effect sizes dependent on study types.

The significant heterogeneity observed in most of the included studies also 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.

The systematic reviews often did not report the methods of measurement of alcohol exposure or the levels of alcohol exposure within the included studies. When methods of measurement were reported these often varied between the included studies. The definitions of alcohol consumption also often varied between the studies and not all of the systematic reviews accounted for this variation sufficiently. Many of the studies identified were not included because the exposure was all alcohol drinking compared to not drinking/occasional drinking, as these did not include varying levels or patterns or alcohol consumption as compared to no alcohol consumption, as per the PEO, and information about levels of alcohol consumption was not analysed and could not be extracted. Some prospective cohorts included relatively low numbers of heavy drinkers, who may be harder to follow-up.

For question one, many of the systematic reviews were also not included due to the exposure not fitting the PEO for question one but the exposure being applicable for question two, for example systematic reviews identified on domestic violence. This issue should be discussed further with the AWC.

Due to the nature of overviews, it is possible that other studies have been published that were not included in the identified systematic reviews.

Gaps identified

The following outcomes and sub-outcomes were searched for where no systematic reviews were identified. It should be noted that these gaps only refer to systematic reviews and no search was undertaken for primary studies.

Figure 69 Outcomes for which no systematic reviews were identified

Question	Outcome
Q1	<i>Hangover</i>
	<i>Acute GI (gastritis, reflux)</i>
	<i>Injury to self or others: Fire/burns</i>
	<i>Injury to self or others: Occupational</i>
	<i>Injury to self or others: Drowning</i>
	<i>Injury to self or others: Poisoning</i>
	<i>Acute cardiovascular events: Cardiac arrest</i>
	<i>Acute cardiovascular events: Arrhythmia</i>
	<i>Cardiovascular disease: Cardiomyopathy</i>
Q2	<i>All-cause morbidity</i>
	<i>Mental health disorders: Anxiety</i>
	<i>Mental health disorders: Alcohol-related psychosis</i>
	<i>Alcohol use disorders/dependence/withdrawal syndrome</i>
	<i>Sleep disorders</i>
	<i>Thiamine deficiency</i>
	<i>Peripheral neurological disorders</i>
	<i>Reflux</i>
	<i>Hormonal disorders</i>
Q3	<i>Neonatal withdrawal</i>
	<i>Developmental delay</i>
	<i>Spontaneous abortion and miscarriage</i>
	<i>Stillbirth</i>
Q4	<i>All outcomes for the population of breastfeeding women</i>

Future research

Systematic reviews of only prospective cohort studies that adjust for the minimum appropriate confounders for that outcome are needed. These systematic reviews should adequately explore identified heterogeneity and conduct assessments of the quality of the included studies. They should also explore potential biases introduced by methods of measurement of alcohol consumption and the choice of reference groups.

Contributions of authors

The following staff of the NHMRC Clinical Trials Centre were involved in planning and conducting the overview, and contributed to the preparation of this report:

Ms Saskia Cheyne	NHMRC Clinical Trials Centre	Scoping and overall design of the research project, development of the research protocol, performed literature searches, review of citations, checking of data, collation of summary data and writing of reports.
Dr Samara Lewis	NHMRC Clinical Trials Centre	Scoping and overall design of the research project, development of the research protocol, performed literature searches, review of citations, checking of data, collation of summary data and writing of reports.
Dr Mark Ayson	NHMRC Clinical Trials Centre	Quality assurance and revisions.
Dr Melina Willson	NHMRC Clinical Trials Centre	Quality assurance and revisions.
Ms Sara Carrillo	NHMRC Clinical Trials Centre	Writing of introduction section.

Declarations of interest

All authors from the NHMRC Clinical Trials Centre declare that they have no financial, personal or professional interests that could be construed to have influenced the conduct or results of this review.

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