Evidence evaluation report

Systematic literature review on the association between alcohol consumption and mental health disorders

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Declarations of interest

The authors of this document have no financial or other perceived or real conflicts of interest pertaining to alcohol or the conditions assessed. The funding for this project was received from the Office of the NHMRC.

Changes from protocol to final report

The protocol allowed for the inclusion of large cross-sectional studies. However, studies without a time element are unable to determine the direction of effect. Given the volume of prospective cohort studies which provided higher level evidence, the decision was made to exclude the cross-sectional studies for all outcomes except suicide/suicidal ideation (which had few prospective cohort studies). Had cross-sectional studies been identified reporting on alcohol related psychoses, they would have been included.

After the finalisation of the protocol, further feedback was received from the Alcohol Working Party that suicide, suicidal ideation and attempts should be included.

Contents

Executive Summary

This systematic review was performed to address the research question of how alcohol consumption influences mood and anxiety disorders. A total of 92 studies were included, the majority of which focused on how alcohol consumption influences subsequent levels of depression/depressive symptoms.

The included studies used many different ways to define the varying levels of alcohol consumption in a single episode or drinking occasion and/or patterns of alcohol consumption over time. Different methods of analysing the available data were also used. These two elements prevented the evidence from being summarised using meta-analyses. The results are therefore synthesised narratively. Studies which used alcohol dependence or alcohol use disorder as the exposure were excluded, as were studies which used questionnaires including these components (such as the AUDIT). This may have resulted in excluding studies which focused on people who drank consistently high amounts of alcohol.

People drink for many reasons, and the relationship between alcohol and mental health outcomes is not consistent across people. This review sought to determine what influence alcohol has on mental health, rather than on how mental health influences alcohol consumption (i.e. drowning their sorrows, or drinking to avoid a negative affect, or to improve affect). Studies which adjusted their results for baseline levels of depression and anxiety were therefore considered to have less risk of bias. Most studies were considered to have a moderate risk of bias. For all outcomes except suicide (suicidal ideation/suicide attempt), only studies with a time-element were included. However, there were prospective cohort studies which also provided cross-sectional correlations between depression and alcohol, and these results were included, in order to aid interpretation of the correlations between baseline alcohol and later depressive symptoms.

Depression

In adolescents, there was consistent evidence of cross-sectional associations between measures of alcohol use (volume consumed, frequency of consumption, frequency x quantity, any alcohol consumed, heavy episodic drinking (HED), heavy or harmful drinking) and depressive symptoms. The evidence regarding alcohol consumption at one time point, and depressive symptoms at a later time point, was less consistent.

A total of 20 studies examined the association between heavy episodic drinking (HED) and depression in the general population. In adolescents, the majority of studies reported that HED predicted increased levels of depressive symptoms (although one study reported that it was associated with a faster decrease of depressive symptoms). This association was found to be stronger in females than males.

In young adults, approximately half of studies which assessed the impact of HED on depressive symptoms or depression, reported a positive association (i.e. the more frequent

the HED, the more likely the young adult would develop depression or have higher symptom levels). Studies which assessed the motives for drinking found them to be vital for interpreting the impact of alcohol (i.e. the impact of drinking socially for pleasure was different to drinking to cope or fit in).

Eight studies were included assessing the effect of alcohol in young adults, five of which assessed alcohol as a predictor variable, other than HED. Neither frequency of alcohol consumption, quantity of alcohol consumed per occasion or quantity x frequency were significantly associated with depressive symptoms or depression.

In adults and older adults, there was some limited evidence that a low amount of alcohol (less than 30 g per day) may be associated with a lower risk of depression than abstinence. Some studies reported non-significant results, but no studies reported harms of alcohol using these categories. Given that there are likely to be systematic differences between those who are completely abstinent and those who drink a low amount (i.e. those who are abstinent may be unable to drink due to health concern, lack of social contact, economic reasons etc.), no conclusions can be made about the benefits of low levels of alcohol.

The evidence on drinking at hazardous or harmful levels (as pre-defined by drinks/day, converted to grams/day) in adults was mixed. Approximately half of studies reported no significant association, while the other half (of a similar risk of bias) reported that hazardous or harmful drinking resulted in higher levels of depressive symptoms or depression.

Suicide

Few prospective cohort studies were identified assessing the impact of alcohol on suicidal ideation or attempts, so case-control studies and large (>1000 participants) cross-sectional studies were also included. In a large cross-sectional study from the United States, an interaction was found between having a major depressive episode (MDE) and HED. In both males and females without a MDE, those who participated in HED were 50% more likely to have suicidal ideation or attempt suicide than their non-HED counterparts. However, there was no difference in those with MDE.

In adolescents, two large cross-sectional studies reported that both HED and drunkenness were associated with suicidal ideation and/or suicide attempt. One of these studies reported that 'drinking while down' (i.e. the motive for drinking) was a stronger predictor of suicide attempt than the drinking of alcohol itself.

Two cross-sectional studies reported consistent evidence that boys and girls who start drinking before age 12 or 13 have a higher risk of having suicidal ideation and suicide attempt than those who had not started drinking alcohol. Those who were drinking as a teenager also had higher suicidal ideation than those who were abstainers. However, initiating of alcohol as a teenager was a significant risk factor for suicide attempt in girls, but not in boys.

One small study in young adults reported that hazardous drinking significantly increased suicidal ideation. A second study reported no direct association between alcohol use (total drinks per week or frequency of HED) and suicide attempts, although there was an indirect effect via depressive symptoms.

One study found no link between alcohol in the bloodstream and completed suicides (as

compared to motor vehicle accidents in a case-control study). A second study in the adult population reported that amount of alcohol consumed per day was associated with suicidal ideation and/or attempts in unadjusted analyses; however, after adjusting for drinking motives, the association was no longer significant.

Anxiety

Three studies assessed the impact of alcohol on anxiety in a wide age-range, and reported no significant relationship was found between high levels of alcohol and the development of anxiety, when baseline levels of anxiety were controlled for. Women who drank outside of guideline recommendations were twice as likely to develop anxiety over the following 5 to 15 years. A single study in adults reported that weekly alcohol was associated with reduced anxiety, compared to drinking less than weekly.

In adolescents, weekly alcohol was deemed to increase the likelihood of developing anxiety, until adjustments for confounding factors such as housing tenures and conduct disorder were made.

Two studies in adolescents found no relationship between total quantity of alcohol consumed (amount per occasion, multiplied by the number of drinking occasions), and subsequent anxiety. A study in adolescent males reported that although drinking frequency made no difference, an increase in the average quantity per occasion was significantly related to a small increase in anxiety.

No relationship was found between the frequency of HED in older adults (aged ≥50 years) and subsequent anxiety.

Subgroups

Evidence was sought on the relationship between alcohol and mental health in a range of subgroups a well as the general population. Although family history of alcohol dependence was occasionally used as a predictor variable, no studies were identified which presented information on how alcohol consumption in individuals with a family history of alcohol dependence influenced their mental health. Likewise, although studies were identified which considered how alcohol dependence was associated with mental health, there were no studies focusing on people with alcohol dependence that used varying levels of alcohol consumption or patterns of alcohol consumption as the predictor variable (i.e. the "exposure" was alcohol dependence, not an alcohol consumption level). Subgroups for which evidence was identified included people with existing mental and physical illnesses (unipolar depression, bipolar depression and HIV), and people receiving medicines or other drugs (cigarettes, marijuana or other drugs).

Studies which looked at how alcohol use influences response to treatment in people with depression were excluded from the systematic review. However, one naturalistic study in people with unipolar depression was included (i.e. not assessing treatment effect). Adolescents with depression were less likely to experience remission if they were weekly drinkers, than if they only drank occasionally or abstained. However, occasional alcohol use did not have an influence on recovery (remission for an extended period).

Two out of three studies in people with bipolar disorder reported that alcohol use was

associated with transition to a depressive episode. However, the remaining study reported no association. Conflicting evidence was also found in two studies on the association between alcohol and the transition to mania or hypomania.

Two studies which focused on either an HIV population, or people with or without HIV, had conflicting evidence regarding whether hazardous or HED influenced depression or depressive symptoms.

Studies which assessed the impact of "substance use" on mental health outcomes were only included if they presented separate information for alcohol as a substance. Three studies were included which discussed the use of alcohol in combination with either cigarettes and marijuana, or "other drugs". Chronic, moderate-to-heavy cigarette, alcohol and marijuana use was associated with over 2.5 times the likelihood of developing depression and anxiety than occasional alcohol use alone. One case-control study assessed whether there were differences in the proportion of adults who had died in a motor vehicle accident, versus suicide, based on whether they alcohol and drugs in their system. The odds of death by suicide was much larger for those who had both alcohol and drugs in their blood stream (OR=4.33) than either alcohol (OR=1.22) or drugs alone (OR=1.03) (Conner et al. 2017).

One study focused on people who were dependent on either alcohol or drugs, and reported that hazardous drinking occasions (over 56 g/day for women or 70 g/day for men) increased the likelihood of depressive and anxiety symptoms (Bahorik et al. 2016).

Seven studies focused on the impact of alcohol on the mental health of people who were exposed to traumas. A single study reported that people who decreased their level of HED after a spinal cord injury were more likely to be depressed than those who never participated in HED. It is possible that those who reduce their HED do so due to reducing their social activities after the injury, or switching to alternative drugs, so no recommendations could be made on the basis of this.

No associations were found between alcohol consumption prior to, or after the trauma, and subsequent PTSD symptoms in college students exposed to trauma, or women exposed to sexual assault.

Summary

The evidence was too inconclusive, to make any definitive statements regarding the risk of alcohol on mental health. Drinking which is classified as 'harmful' or 'hazardous' may negatively impact on mental health, particularly in younger age-groups (although these findings were not consistent). Some studies showed that those who adults and older adults who abstain had worse mental health than those who consumed a small amount of alcohol, but the studies were unable to determine the reason for this.

Abbreviations

Abbreviation	Full name
95%CI	95% confidence interval
AHTA	Adelaide Health Technology Assessment
AUDIT	Alcohol Use Disorders Identification Test
AWC	Alcohol Working Committee
CAPS	Clinician-Administered PTSD scale
GAD	generalised anxiety disorder
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HED	heavy episodic drinking
HR	hazard ratio
MDD	major depressive disorder
MDE	major depressive episode
N	number of participants in the study
NHMRC	National Health and Medical Research Council
OR	odds ratio
PECO	Population, Exposure, Comparator, Outcome
PTSD	post-traumatic stress disorder
r	Pearson correlation
REF	reference category (for odds ratio or hazard ratio)
rho	Spearman correlation
RR	relative risk

1 Introduction and background

In 2007, the National Survey of Mental Health and Wellbeing (SMHWB) found that one in five Australian aged 16-85 had a 12-month mental disorder (ABS 2008), and almost half (45%) had a lifetime mental disorder (i.e. a mental disorder at some point their lifetime). Mental disorders are categories into three main categories: anxiety disorders (e.g. generalised anxiety disorder, social phobia, post-traumatic stress disorder), affective disorders (e.g. depressive episode, dysthymia and bipolar disorder) and substance use disorders (e.g. alcohol harmful use, alcohol dependence and drug use disorder).

Mental health and mental illnesses are influenced by a range of different interacting social, psychological and biological factors, such as social support, household income, level of education, country of birth, and marital status. Health risk factors which have been found to either positively or negatively influence mental health are physical activity, overweight or obesity, tobacco use (smoking), misuse of drugs and alcohol consumption (ABS 2008).

Alcohol consumption may interact with mental health in a variety of ways, including:

- People with mental health disorders are more likely to experience problems related to alcohol; and
- People with Alcohol Dependence are more likely to also have other mental health problems (Boden & Fergusson 2011).

Although existing systematic reviews exist which discuss the relationship between alcohol use disorder and mental health, there is currently very little synthesised evidence on how different levels of alcohol consumption influence mental health. This question is of interest to the National Health and Medical Research Council (NHMRC), who are revising their 2009 Alcohol Guidelines.

Under Section 7 of the *National Health and Medical Research Council Act 1992*, NHMRC has responsibility for providing high quality evidence based health advice to government and the Australian community.

Revision of the 2009 Alcohol Guidelines

In March 2009, NHMRC released the 2009 Alcohol Guidelines, providing policy makers, health professionals and the Australian community with updated advice on the health risks of drinking alcohol. The 2009 Alcohol Guidelines provide universal guidance on reducing these risks to healthy adults aged 18 years and over (Guideline 1 and 2), plus guidance specific to children and young people (Guideline 3) and to pregnant and breastfeeding women (Guideline 4).

NHMRC regularly reviews its guidelines to ensure that the advice is up to date and reflective of the latest evidence. In March 2015, the Council of NHMRC recommended to NHMRC's Chief Executive Officer that the 2009 Alcohol Guidelines be updated. The 2009 Alcohol Guidelines will remain NHMRC's current advice until this revision is complete.

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

The revision of the 2009 Alcohol Guidelines focusses on the short and long term health risks and benefits of various levels and patterns of alcohol consumption on the general population and various population subgroups.

In October 2016, ONHMRC commissioned an independent evaluation of the evidence on the health effects of alcohol consumption. The evidence evaluation comprised four overviews of systematic reviews (the overview), addressing four research questions formulated by the AWC. The overview identified and evaluated systematic reviews published since 1 January 2007.

Following consideration of the overview report, AWC members advised that, for certain research questions, there was insufficient evidence to support decision making for drafting guideline recommendations.

To supplement the overview and support decision making for drafting guideline recommendations, the AWC prioritised mental health disorders as a critical[1] health outcome for an additional systematic review of primary research.

NHMRC's Standards for Guidelines (Appendix A) ensure that the scientific evidence is correctly and appropriately analysed, interpreted and presented, and provides reassurance that the revised Guidelines have been developed in a rigorous and transparent manner.

To meet NHMRC's standards, the evidence evaluation must include a well performed systematic review. This means that the review should include:

- Comprehensive and clearly defined search strategies and pre-specified study inclusion and exclusion criteria.
- Critical appraisal of the quality of the included studies, including an assessment of the risk of bias.
- The application of standard methods to assess the body of evidence, such as GRADE[2].

Adelaide Health Technology Assessment (AHTA), University of Adelaide, have been contracted by the Office of the National Health and Medical Research Council (ONHMRC) to conduct a systematic literature review on the latest and best scientific evidence on the mental health effects (risks and benefits) of alcohol consumption.

1.1 Objectives of the systematic literature review

The systematic review comprehensively searched for, collated, analysed and synthesised the results of primary studies which reported on the association between various levels and/or patterns of alcohol consumption and the mental health outcomes of interest, focusing on studies published since January 2007[3].

The systematic review addressed the following research question:

1. What is the **association** between various levels and/or patterns of **alcohol consumption** and chronic **mental health disorders** (mood disorders[4] and anxiety disorders[5] are the main outcomes of interest) in the general population and various subgroups:
    - By age group
    - By sex and/or gender
    - People with existing physical and/or mental health conditions
    - People with a family history of alcohol dependence

[1] This outcomes was rated as critical for decision making by the AWC during the classification of the importance of outcomes for the overview, using GRADE.

[2] GRADE = Grading of Recommendations. Assessment, Development and Evaluations

[3] Consistent with the date that last literature searches were undertaken for the 2009 Alcohol Guidelines

[4] "Those disorders that have a disturbance in mood as their predominant feature" – MeSH Descriptor Data 2018, https://meshb.nlm.nih.gov/record/ui?ui=D019964

[5] "Persistent and disabling anxiety" – MeSH Descriptor Data 2018, https://meshb.nlm.nih.gov/record/ui?ui=D001008

- People using licit and/or illicit drugs

2 Review methodology

A systematic review was performed in order to summarise the best available evidence on the association between alcohol consumption and mental health outcomes. The methods for the systematic review are described in detail in the Technical report.

Bibliographic databases were searched (PubMed, Embase.com, Cochrane Library, CINAHL and PsychInfo) for relevant articles. Studies meeting inclusion criteria determined *a priori* were independently assessed for inclusion by two reviewers. For the initial screen, articles which either reviewer included were retrieved for full text assessment. Any disagreements regarding inclusion of full text articles were discussed, and a consensus view formed.

The PECO framework guiding the systematic review question is presented in Table 1.

Table 1 PECO criteria for the evaluation of association between alcohol consumption and mental health disorders

Element	Criteria
Population	The general population If evidence is identified, the following specific subpopulations will be examined: Sex Elderly (people ≥65 years) Youth (people < 18 years and between 18 – 25 years) People with existing mental and physical illnesses People with existing alcohol dependence People with strong family history of alcohol dependence People on medicines or other drugs (prescribed and illicit) including interactions
Exposure	Varying levels of alcohol consumption in a single episode or drinking occasion and/or patterns of alcohol consumption over time
Comparator	Reference level and/or pattern of alcohol consumption (including no alcohol consumption)[a]
Outcomes	Critical: Chronic mental health disorders (depression, anxiety, alcohol-related psychosis) Important: depressive symptoms, symptoms of anxiety, suicidal ideation/suicide attempts/completed suicide

[a] Reference groups may consist of occasional drinkers, lifetime abstainers or current abstainers, which may include former drinkers.

2.1.1 Definitions of alcohol exposure

The exposure variable of interest was "varying levels of alcohol consumption in a single episode or drinking occasion and/or patterns of alcohol consumption over time". There was little consistency between studies in regards to how they defined varying levels or patterns of alcohol consumption.

Among the included studies, alcohol consumption was defined as:

- Dichotomous: no alcohol vs alcohol;
- Volume of alcohol consumed in a set time period (e.g. average number of 'standard drinks' per day, week, month or year).
- Frequency of alcohol consumption (e.g. daily, weekly ,monthly, occasional drinkers)
- A composite score that provides a measure of both quantity and drinking frequency, used as a continuous variable
- An AUDIT-C score for low risk and high risk alcohol consumption levels

The volume of alcohol consumed over a set time period was either used as a continuous variable or participants categorised into groups. The alcohol quantity cut-offs varied greatly between studies, and although different studies tended to define groups using similar terms such as light, regular or moderate, and heavy or excessive drinkers, the average amount of alcohol consumed daily varied greatly and made comparisons between studies difficult. Studies that categorised participants according to frequency of alcohol consumption did not take differing levels of consumption per 'drinking day' or occasion into account, resulting in heterogenic groups.

Studies reporting on heavy episodic drinking (HED) provide an excellent example of the heterogeneity between cut-off in different studies. The definition of HED varied between 4 and 6 drinks per session (or day). The studies also varied according to the time period over which HED occasions were reported from one week, to one month or even one year. Some studies applied the same cut-off to both men and women, whereas other studies had a lower cut-off for women compared to men. Furthermore, all except one of these studies did not take the different frequency of HED among the study participants into account. One study further divided those participating in HED into those who participated less than once a month and those who participated at least once a month.

The majority of studies that reported the volume of alcohol consumption used 'standard drinks' as the unit of measurement. However, the size of a standard drink varies between countries. For this reason, the results in this systematic review have been converted to grams of alcohol. Table 2 lists the quantity of alcohol in 'one standard drink' for each of the countries from which the source populations of the included studies were derived. These quantities were used for conversion unless a differing definition of a standard drink was reported in the study.

Table 2 Grams of alcohol per standard drink in the different countries in which the studies included in this review were conducted

Country	Alcohol (g) in one standard drink
Australia	10 g
Brazil	14 g
Canada	~13.6 g
China	10 g
Denmark	12 g
Finland	12 g
Germany	10 g
Ghana	10 g
India	10 g
Italy	10 g
Japan	19.75 g
Kiribati	10 g
Korea	8 g
Mexico	14 g
Netherlands	10 g
Norway	12 g
Russia	~16 g
Samoa	10 g
Solomon Islands	10 g
Spain	10 g

Country	Alcohol (g) in one standard drink
Sweden	10 g
Switzerland	10 g
Taiwan	NA
Unite Kingdom	8 g
United States	14 g
Vanuatu	10 g

2.1.2 GRADE framework for synthesis and interpretation of the body of evidence

For each identified mental health outcome, the quality of the evidence contributing to that outcome was assessed using GRADE. The GRADE approach involves considering the study design, the risk of bias, directness of evidence, inconsistency (heterogeneity), precision of effect estimates and risk of publication bias (and other biases) for each outcome, resulting in an overall quality of evidence depicted using the ⊕ symbol, with four ⊕ indicating high quality, and one ⊕ indicating very low quality. A Summary of Findings table containing the GRADE output was constructed (Guyatt et al. 2013), and an evidence statement developed, reflective of the GRADE or confidence in the reported findings for each outcome, to be considered by the AWC and the ONHMRC.

The first step in the GRADE process is to identify whether the evidence was derived from a randomised controlled trial or other study types. Observational study designs are normally rated down by two points to 'low', due the additional uncertainty of conclusions from observational studies, as compared to randomised trials. However, given the research question, a randomised design was not likely (e.g. randomisation to large consumption of alcohol), and so prospective cohort studies were considered the most appropriate design. These were therefore only rated down one point to 'moderate' quality rather than 'low' quality, and 'moderate' was used as the starting point for the quality of evidence and either upgraded or downgraded depending on the methodological characteristics of the evidence base (see Technical Report for further information). The approach was consistent with that used in the 2017 Alcohol Guidelines report, as agreed to by NHMRC and the AWC (NHMRC Clinical Trials Centre 2017).
Evidence statements derived from findings in the evidence base adopted consistent language to reflect the GRADE components. The Evidence Statements generally fit into one of the following categories:

I. *Consistent evidence of an association* – this wording was used when the body of evidence was deemed valid and at low risk of bias (⊕⊕⊕⊕ or ⊕⊕⊕⊖), applicable to the Australian context and consistently showed an association between alcohol consumption and mental health outcomes (i.e. there was more than one study). If the evidence was rated as ⊕⊕⊕⊖ and there was only study, the statement was amended to "*There was evidence of an association".*
II. *The evidence shows no association* – this wording was used when the body of evidence was deemed valid and at low risk of bias (⊕⊕⊕⊕ or ⊕⊕⊕⊖), applicable to the Australian context, and demonstrated that there was no association between alcohol consumption and mental health outcomes.
III. *Limited evidence of an association* – this wording was used when it was deemed that there is limited confidence that the body of the evidence shows an association between alcohol consumption and mental health outcomes applicable to the Australian context. The lack of confidence could be due to either the risk of bias in the studies, or heterogeneous results between studies.

IV. *No reliable evidence of an association* – this wording was used when the body of evidence could not confidently be deemed sufficiently valid or relevant to the Australia context, such that the level of association between alcohol consumption and mental health outcomes cannot be determined. Confidence in the body of evidence can be affected by several issues including the small number of studies, the study designs, the low quality of the studies and the lack of control for possible confounding factors. Confounding factors can include lack of consideration of: baseline physical and mental health status, age, sex, marital status, socioeconomic status, life events, occupation, type of area (urban/rural), presence of support group, smoking behaviour, illicit drug use, use of psychotropic drugs or therapy, and treatment for pre-existing mental health problems.

3 Results – General Population

Results for the general population (i.e. studies which do not fit subgroups, other than age or gender based subgroups) are presented in Section 3, divided by outcome (i.e. depression, suicidality, anxiety, psychosis). The 'All ages' category includes those studies which fit into more than one age subgroup (i.e. including both adolescents and adults, or including both younger and older adults, or all three).

3.1 The effect of alcohol consumption on developing depression and depressive symptoms (general population)

3.1.1 All ages

Summary:

Both genders combined:

Three studies were consistent that no association was found between low levels of drinking (drinking within guidelines or non-excessively) and likelihood of depression 5-8 years later. However, this evidence was at risk of bias, was not deemed highly applicable to Australia, and was rated down for imprecision.

Only out of three studies reported an association between excessive drinking (exceeding guidelines), and likelihood of depression, meaning the evidence was inconclusive.

Evidence from three studies was identified regarding whether heavy episodic drinking (HED) versus either non-HED or abstinence was associated with a higher likelihood of depression or not, with one study reporting a statistically significant effect, and two studies supporting the null hypothesis.

Drinking on a weekly, monthly or occasional basis (at levels not considered to be hazardous), was found to be associated with less risk of depression in three studies, and harmful in one. No conclusions about occasional low-level drinking can therefore be made.

In females:

A single study showed no association between drinking frequency or drinking more or less than 10 g per day on the rate of women developing depression at a later time point. One study reported that those who drank monthly had less chance of depression than abstainers, while those who drank occasionally had more chance of depression. A single study reported a positive association between hazardous drinking and depressive symptoms after 4 years.

In males:

Three studies provided consistent evidence that males drinking above particular thresholds (5 or 9 drinks per week, or AUDIT-C score 4) did not have a significantly increased likelihood of having depression compared to those drinking below the thresholds. Two studies were consistent that men who drank more than once per month were less likely to have depression at follow-up, than those who abstained or drank less regularly. One of these studies also reported that those who drank occasionally had significantly more chance of depression at follow-up than those who abstained.

Twelve longitudinal cohort studies reported on the likelihood of developing either depressive symptoms or having a depressive episode as a consequence of alcohol intake in individuals aged 12 years and older. Four studies included all ages from adolescents to older adults and eight studies included adults of all ages. Two of the studies did not report the age range of included participants, but as they were likely to include adults of all ages and had a mean age was 51 and 56 years, these

studies were included in this section. Six studies provided data for males and females separately. The risk of bias for the studies reporting outcomes for the total population, and for males and females separately, are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 1. The majority of the studies had a low or moderate risk of bias for both the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and its generalisability to the broader population from which the study participants were selected. However, half of the studies reporting outcomes for males had a high risk of bias for internal validity.

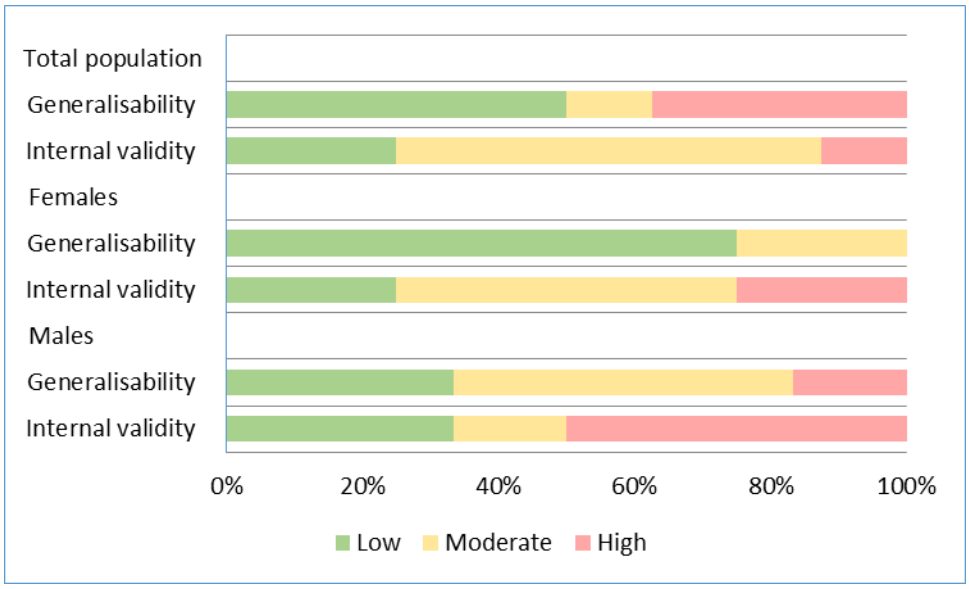


Figure 1 Risk of bias summary for studies reporting depression outcomes for individuals who drank alcohol
Eight studies included results for the total population, four studies included results for females and six studies included results for males.

3.1.1.1 Combined gender

Five studies reported on the likelihood of developing depression according to the quantity of alcohol consumed (Figure 2). Two of these studies used the abstinent group, two used abstinent and guideline drinkers and the fifth study used only guideline (or non-hazardous) drinkers as the reference groups. In order to allow some comparison between the studies, the categories from these studies were converted to g alcohol/day.

Cabello et al. (2017) categorised participants from Ghana, India, Mexico and Russia, aged ≥18 years, into never drinkers, non-heavy drinkers and heavy drinkers defined as having at least 5 (for men) or 4 (for women) standard drinks on at least one day in previous week. The definition of a standard drink was country-specific, with a net alcohol content range of 10−16 g. Thus, heavy drinkers were assumed to have consumed at least 50 g (for men) or 40 g (for women) of alcohol on at least one day in previous week. The number of participants in each drinking category was not reported. The authors reported no significant differences in the likelihood of developing depression between the drinking groups. Van Gool et al. (2007) enrolled Dutch adults aged 24−81 years and divided the participants into three groups: non-drinkers, regular drinkers consumed ≤2 drinks/day, and excessive drinkers drank ≥3 drinks/day. One standard drink in the Netherlands contains 10 g of alcohol. They found that those who drank ≥3 drinks (30 g alcohol)/day were 2.5-times more likely to develop a depressed mood 6 years later.

Bulloch et al. (2012) defined Canadian participants, aged ≥12 years, as excessive drinkers who exceeded moderate drinking guidelines (14 drinks [190 g alcohol] in a week for men and 7 [95 g] for

women) in the past 7-days. In Canada, a standard drink contains about 13.6 g of alcohol. Heavy episodic drinking (HED) was defined as ≥5 drinks (68 g alcohol) on one occasion during the past 7-days. The group who were either abstinent or drank within the guidelines were used as the reference group, but the number of participants in each group were not reported. No significant differences in the likelihood of having a major depressive episode (MDE) between the drinking groups were identified. This differed from Sullivan et al. (2011) who used similar cut-offs. Sullivan et al. (2011) enrolled American veterans aged 22−87 years, and defined HED as consuming 6 or more drinks (a total of 84 g alcohol) on one occasion, 3 or more times during past year and non-hazardous drinking as consuming alcohol in the previous year but not HED or hazardous drinking. The authors used the non-hazardous drinkers as the reference group and found that the likelihood of participants of HED developing MDD was 2.1-times higher than for non-hazardous drinkers. There was a non-significant difference in likelihood of developing MDD between non-hazardous drinkers and former drinkers.

Magnusson Hanson et al. (2016) reported on the association between excessive alcohol consumption and depressive symptoms 6 years later in individuals aged 16−64 years. Excessive alcohol use was defined as ≥21 (for men) and ≥14 (for women) standard drinks weekly or drinking ≥6 drinks per occasion at least weekly. The standard drink in Sweden is equivalent to 12 g of alcohol. Thus excessive drinking was considered to be the consumption of ≥36 g of alcohol/day for men and 24 g/day for women. The authors found the relationship between excessive alcohol consumption in 2008 and depressive symptoms two years later, which was reported as a β coefficient, was not significant.

The alcohol categories from these five studies were graphed to show the overlapping alcohol consumption groups (Figure 2) and the HED groups (Figure 3) so that the results could be compared. The only statistically significant outcome was reported by Sullivan et al. (2011) and Van Gool et al. (2007).

Four of the five studies were conducted in countries which would provide evidence applicable to the Australian setting. The fifth study by Cabello et al. (2017) included participants from Ghana, Mexico, India and Russia; the drinking cultures in these countries may not be directly applicable to the Australian setting. The internal validity of the study by Van Gool et al. (2007) was moderate, and the authors found that excessive drinking was associated with a significantly higher likelihood of depression. Two additional studies, with moderate (Bulloch et al. 2012) or poor (high risk of bias; Magnusson Hanson et al. 2016) internal validity, found no difference between drinkers that did or did not exceed drinking guidelines. There was no difference between regular drinkers, non-heavy drinkers or former drinkers and the reference group in the likelihood of developing depression. Although the studies were consistent that there was no association between low levels of drinking and depression, a strong conclusion of no effect has not been made, given the risk of bias and possible lack of generalisability of the evidence to the Australian population. It is therefore concluded that there was *no reliable evidence of an association* between excessive drinking and depression 5−8 years later (GRADE ⊕⊖⊖⊖). There was also *no reliable evidence of an association* between regular drinkers or former drinkers and depression.

Van Gool et al. (2007) also reported the RR (95% CI) of having a depressed mood at follow-up as a consequence of transitioning in drinking behaviour between baseline and follow-up. The authors used those who remained abstinent as the reference group. They reported that participants who initiated alcohol use during the follow-up period were 5-times less likely to have a depressed mood than those who remained abstinent (RR=0.18, 95% CI 0.04, 0.76, $p<0.05$). Participants who still drank alcohol and those who quit drinking alcohol were equally likely to have a depressed mood as participants who were abstinent (RR=0.80, 95% CI 0.45, 1.41 and RR=1.29, 95% CI 0.57, 2.91, respectively).

Thus, there is *limited evidence of an association* between HED and depression at a later time point (GRADE ⨁⨁⊖⊖).

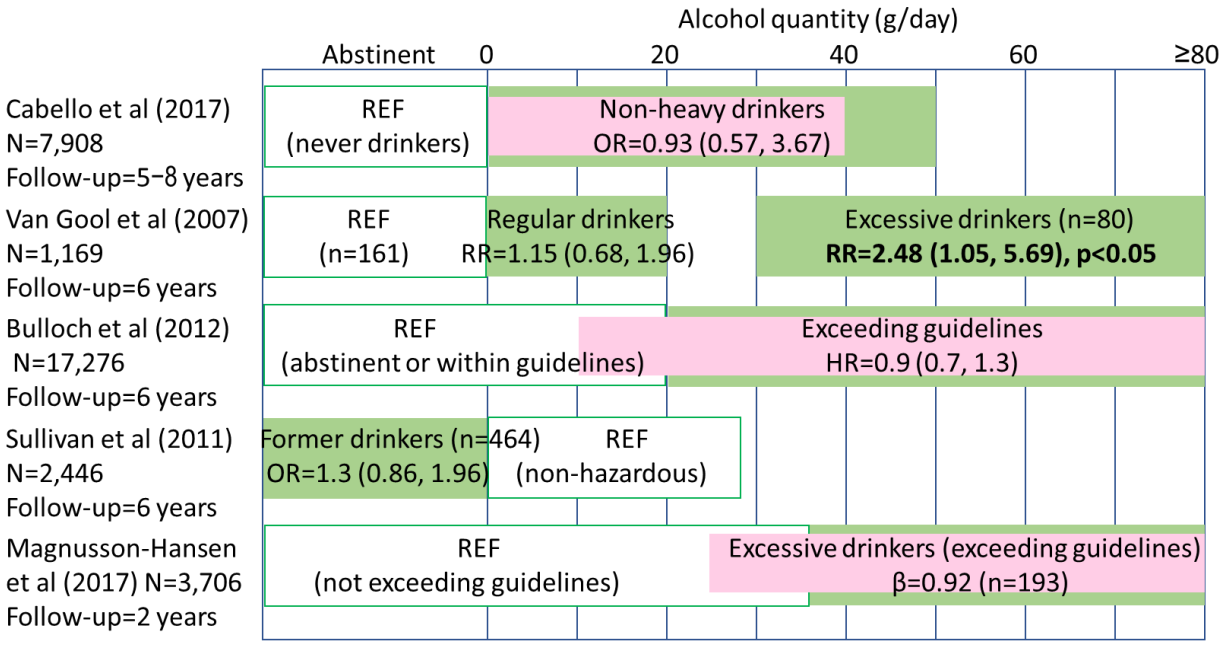


Figure 2 Graph depicting the OR, HR, RR, and the 95% CIs or the β coefficient, for the likelihood of having either depression or a depressed mood among adults according to their drinking quantity 2−8 years earlier compared with the reference group

The green bars represent the number of drinks/day included in each drinking category. The pink bars represent the number of drinks/day included for females if this differed from the males. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each group has been included for those that were reported. Bulloch et al. (2012): HRs adjusted for gender, age, marital status, employment status, having a chronic condition, being in pain and having a low income. Cabello et al. (2017): ORs adjusted for demographics, presence of physical chronic condition, BMI, general health status and country. Sullivan et al. (2011): ORs adjusted for correlated outcome data, gender, race, and age. Van Gool et al. (2007): RRs adjusted for baseline depressive symptomatology, age, gender, marital status, educational level, instrumental activities of daily living status, and number of chronic diseases.

The heavy drinking category from the study by Cabello et al. (2017) described maximum drinking quantities on a given day rather than per day, thus it is more comparable to HED outcomes and was included in the HED analysis (Figure 3). The point estimates for all three studies reporting on HED outcomes showed an increased likelihood of having depression 5−8 years later compared to the reference group. However, only one study showed a statistically significant increased risk. Thus, it is concluded that there is *no reliable evidence of an association* between HED and depression at a later time point (GRADE ⨁⊖⊖⊖).

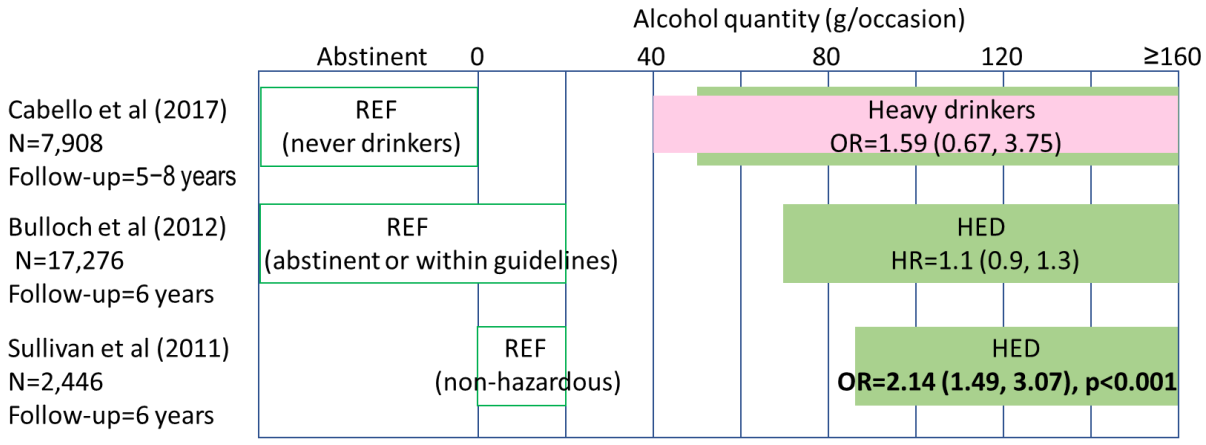


Figure 3 Graph depicting the OR and HR, and the 95% CIs, for the likelihood of having either depression or a depressed mood in participants of HED 5−8 years earlier compared with the reference group

The green bars represent the number of drinks/day included in each drinking category. The pink bars represent the number of drinks/day included for females if this differed from the males. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each group was not reported in these studies. Cabello et al. (2017): ORs adjusted for demographics, presence of physical chronic condition, BMI, general health status and country. Sullivan et al. (2011): ORs adjusted for correlated outcome data, gender, race, and age. Van Gool et al. (2007): RRs adjusted for baseline depressive symptomatology, age, gender, marital status, educational level, instrumental activities of daily living status, and number of chronic diseases.

Three studies with moderate internal validity that were conducted in the United States or Canada reported on the likelihood of developing depression within 2-16 years as a consequence current drinking frequency and all outcomes were statistically significant (Table 3). Cougle et al. 2015, included adults aged ≥18 years and found that the likelihood that weekly drinkers would develop depression within 3 years was 12% less than for people who drank less than weekly. Meng (2017) included participants aged ≥12 years and reported that people who drank at least once a month were 12% less likely to have an MDE over the next 16 years than less than monthly drinkers and never drinkers. Meng et al. (2017) included participants aged 15−65 years and reported that former drinkers and at least monthly drinkers had a reduced risk of developing MDD within 4 years compared with never drinkers. Occasional drinkers had up to 56% greater chance of developing depression than never drinkers. The evidence is considered too uncertain to make any conclusions regarding the optimal frequency of alcohol consumption (GRADE ⨁⊖⊖⊖).

Table 3 The OR, HR or RR and the 95% CIs for the likelihood of developing depression within 2−16 years in people according to their drinking frequency

	Time period	Never drinker	Former drinkers	Occasional drinker	Monthly drinker	Weekly drinker
Cougle et al. (2015) N=34,653	3 years	REF				**OR=0.88 (0.83, 0.94), p<0.001**
Meng (2017) N=12,227	16 years	REF			**HR=0.88, (0.778, 0.995), p=0.041**	
Meng et al. (2017) N=1,212	2 years	REF	**RR=0.15 (0.12, 0.19), p<0.001**	**RR=1.28 (1.12, 1.45), p<0.001**	**RR=0.51 (0.44, 0.58), p<0.001**	
N=877	4 years	REF	**RR=0.28 (0.23, 0.33), p<0.001**	**RR=1.56 (1.40, 1.75), p<0.001**	**RR=0.68 (0.61, 0.76), p<0.001**	

Cougle et al. (2015): OR adjusted for age, income, marital status, gender, ethnicity, education, and psychiatric comorbidity. Meng (2017) and Meng et al. (2017) did not adjust for any possible confounders. The number of participants in each drinking category were not reported for these studies. The green shading represents statistically significant results.

3.1.1.2 Female and male subgroup analysis

Three studies conducted in the United States looked at the likelihood of developing depression according to alcohol consumption quantity in men and women separately; two with a good internal validity (low risk of bias; Ruggles et al. 2017; Sui et al. 2009) and one with poor internal validity (Onwuameze et al. 2013).−Sui et al. (2009) enrolled healthy (no mental/mood disorders, cardiovascular disease or cancer at baseline) men and women aged 20−81 years and reported on the effects of drinking ≥5 drinks (≥70 g alcohol)/week compared with <5 drinks/week on the likelihood of developing depression within 12 years in males and females (Figure 4). The authors found no difference in the likelihood of developing depression between those who drank more than 5 drinks/week and those who drank less for either males or females (GRADE ⨁⨁⨁⊖).

Onwuameze et al. (2013) enrolled farmers from Iowa (98% male) with a mean age 56 years (age range not reported), and compared the likelihood of developing depression over 3 years between

those who drank more than 9 alcoholic drinks (126 g alcohol)/week and those who drank less. Ruggles et al. (2017) included older veterans with a mean age of 51 years (age range not reported) and used an AUDIT-C cut-off of ≥4 for unhealthy alcohol use. The three AUDIT-C questions that measure the amount and frequency of a person's drinking and this score represents hazardous drinking levels, or drinking that exceeds guideline recommendations. The US guidelines recommend 1 standard drink (14 g alcohol) per day for women and 2 drinks per day for men (28 g alcohol). The likelihood of developing MDD in unhealthy drinkers was compared to healthy drinkers.

Daily alcohol consumption was graphed to compare outcomes for males and females (Figure 4). As all three studies were conducted in the United States among, farmers, veterans and the general population, these studies are likely to be applicable to similar populations in Australia. None of these three studies showed a statistically significant association between alcohol consumption and the development of depression. There is *no reliable evidence of an association* between drinking more than 10−30 g alcohol/day and depression at a later time point when compared with drinking less (GRADE ⨁⨁⊖⊖).

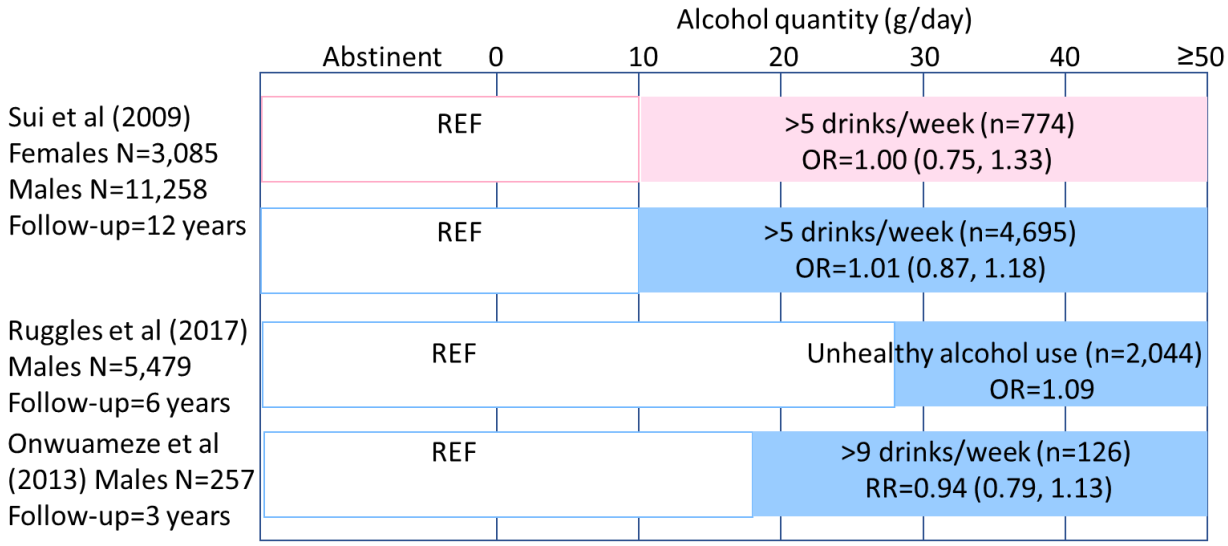


Figure 4 Graph depicting the RR or HR and the 95% CIs for the likelihood of having depression among participants who drank ≥5 drinks/week 12 years earlier compared with those who drank <5 drinks/week

The pink and blue bars represent the number of drinks/day included for in each drinking category females and males, respectively. The 95% CIs are shown in brackets. The number of participants included in the drinking group are shown. Sui et al. (2009): OR adjusted for age, baseline examination year and survey response year. Onwuameze et al. (2013): univariate analysis. Ruggles et al. (2017): OR adjusted for number of years from enrolment, depression status at baseline, current alcohol use, smoking, and for stimulant use.

Two Canadian studies with moderate internal validity, enrolling adolescents and adults of all ages, reported on the effect of drinking frequency on developing depression 2−16 years later for females or males (Table 4). Meng (2017) found that males who drank more than once per month were 21% less likely to develop depression over the next 16 years than males who drank less often. There was no difference between the two groups for females. Meng et al. (2017) found that males and females who were former drinkers or more than once monthly drinkers were 1.5- to 10-times less likely to develop depression within 4 years than never drinkers. They also found that both male and female occasional drinkers were 1.2- to 2.6-times more likely to develop depression within 4 years than never drinkers.

The evidence is considered too uncertain to make any conclusions regarding the optimal frequency of alcohol consumption (GRADE ⨁⊖⊖⊖).

Table 4 The HR or RR and the 95% CIs for the likelihood of developing depression within 2−16 years in males and females according to their drinking frequency

	Follow-up	Never drinker	Former drinkers	Occasional drinker	Monthly drinker
Meng (2017)					
Women N~6,334	16 years	REF			HR=0.92 (0.80, 1.05)
Men N~5,893	16 years	REF			**HR=0.79 (0.64, 0.98), p=0.035**
Meng et al. (2017)					
Women N=646	2 years	REF	**RR=0.11 (0.07, 0.15), p<0.001**	**RR=1.49 (1.25, 1.77), p<0.001**	**RR=0.75 (0.63, 0.89), p=0.001**
Women N=550	4 years	REF	**RR=0.21 (0.17, 0.27), p<0.001**	**RR=1.19 (1.05, 1.35), p=0.008**	**RR=0.75 (0.66, 0.85), p<0.001**
Men N=327	4 years	REF	**RR=0.26 (0.18, 0.37), p<0.001**	**RR=2.62 (1.93, 3,56), p<0.001**	**RR=0.45 (0.33, 0.62), p<0.001**

Blue and pink cells represent statistically significant results for males and females, respectively. Meng (2017) and Meng et al. (2017) did not adjust for any possible confounders. The number of participants in each group was not reported.

One small study by Johnson et al. (2013) with poor internal validity, enrolled 382 women aged 18−83 years and found a significant positive association between HED and depressive symptoms 4 years later (Table 5). HED was defined by a combination of drinking ≥6 drinks (84 g alcohol)/occasion and subjective intoxication over the previous 12 months (GRADE ⊕⊖⊖⊖). The study was considered too small on which to base firm conclusions. It is therefore concluded that there is *limited evidence of an association.*

Table 5 The correlation between mean number of drinks consumed and depression symptoms within 4 years

Population	Exposure	Follow-up	Results
N=384 Adult females (18-83 years)	≥6 drinks/week, or been drunk ≥1 occasion past year (n=98)	4 years	β=0.18, p<0.05

Source: Johnson et al. 2013

The regression analysis was adjusted for baseline depressive symptoms.

3.1.2 Adolescents

Summary:

Both genders combined:

Cross-sectional associations between measures of alcohol (volume consumed, frequency of consumption, frequency x quantity, any alcohol consumed, HED, heavy or harmful drinking) and depressive symptoms were all consistently statistically significant in adolescents. However, cross-sectional data do not allow conclusions regarding the direction of effect to be made. Studies regarding prospective associations between alcohol measures at one time point, and depressive symptoms at a later time point, controlling for baseline depression, were much less consistent.

Two studies reported on an association between volume of alcohol consumed and levels of depressive symptoms a year or two later. The larger study reported all correlations were significant, while the smaller study showed an effect in the same direction but was not statistically significant.

Three out of four studies reporting on the association between frequency of alcohol consumption and depressive symptoms found significant positive correlations, but after adjusting for gender, generational

status, and delinquency, one of the studies found the association was no longer significant. The fourth study reported non-significant results in the opposite direction.

Two out of three studies reported an association between alcohol quantity x frequency and depressive symptoms. The remaining study had results in the same direction but was too small for the results to be statistically significant.

Two studies reported on an association between the consumption of any alcohol and depressive symptoms up to 3 years later. Both studies reported positive associations between adolescents (aged 11 – 14 years) drinking any alcohol (more than a few sips) and depression at later time points. One study reported that correlations were not significant for depression at age 13, but the study was underpowered.

One study reported adolescents who drank weekly at age 13, were more likely to have depressive symptoms at ages 15 – 18 compared with those who drank less than weekly. Those who were less than weekly drinkers at age 13 but increased their consumption such that they were weekly drinkers by age 18 were also more likely to have depressive symptoms at ages 18 compared with those who drank less than weekly between the ages of 13 and 18.

Six studies reported on an association between HED or drinking to intoxication and depressive symptoms. The majority of the studies showed a positive association between HED and later depressive symptoms (up to 6 years). However, one study found negative associations, suggesting that HED may result in fewer depressive symptoms. The reason for the heterogeneity is unclear.

In females:

One study reported that HED more frequently than once per week when aged 16-21 was significantly associated with having depression between ages 22 and 27. Weekly HED or less was not associated with depression.

One study reported that 14-year-old girls who drank moderately (occasionally) or highly (weekly) were significantly more likely to have a depressive episode at age 16 than those who drank only occasionally or not at all.

Two studies reported no significant association between frequency of alcohol consumption and depressive symptoms, although a consistent positive trend was identified.

A single small study reported on the association of quantity x frequency and depressive symptoms after 1 and 2 years. The correlations were significant at nearly all time points, suggesting that in females, the number of drinks consumed in a month over ages 12 – 14 predict depressive symptoms a year or two later.

Four studies reported conflicting results for the association between HED and depressive symptoms. One study reported that those participating in HED had higher concurrent levels of depressive symptoms. Age-related reductions in depressive symptoms were therefore larger on average for those who participated in HED at baseline (i.e. HED predicted a faster reduction in symptoms, which may be due to regression to the mean). One study reported that HED was associated with higher depressive symptoms at follow-up, while the remaining two studies reported no association.

In males:

One study reported that moderate (occasional) and high (weekly) levels of alcohol consumption in 14 -year -old males, significantly predicted having a depressive episode by age 16.

Two small studies found no significant association between frequency of alcohol consumption and depressive symptoms.

Another small study reported on the association of quantity x frequency and depressive symptoms after 1

and 2 years. Only one correlation out of six was significant, suggesting that overall, the number of drinks consumed in the past month does not predict depressive symptoms.

Four studies reported on the association between HED and depressive symptoms up to 14 years later. As per female adolescents, one study reported that HED was associated with a faster reduction in depressive symptoms, one reported it was associated with higher depressive symptoms, while the remaining two studies reported no association.

Twenty-two longitudinal cohort studies, including three studies conducted in Australia, reported on the likelihood of developing either depressive symptoms or having a depressive episode as a consequence of alcohol intake in adolescents aged between 11 years and 17 years. Nine of these studies reported depression outcomes for girls, and eight reported outcomes for boys. The risk of bias for the studies reporting outcomes for the total population and for males and females separately, are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 5. The majority of the studies had a low or moderate risk of bias for both the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and its generalisability to the broader population from which the study participants were selected.

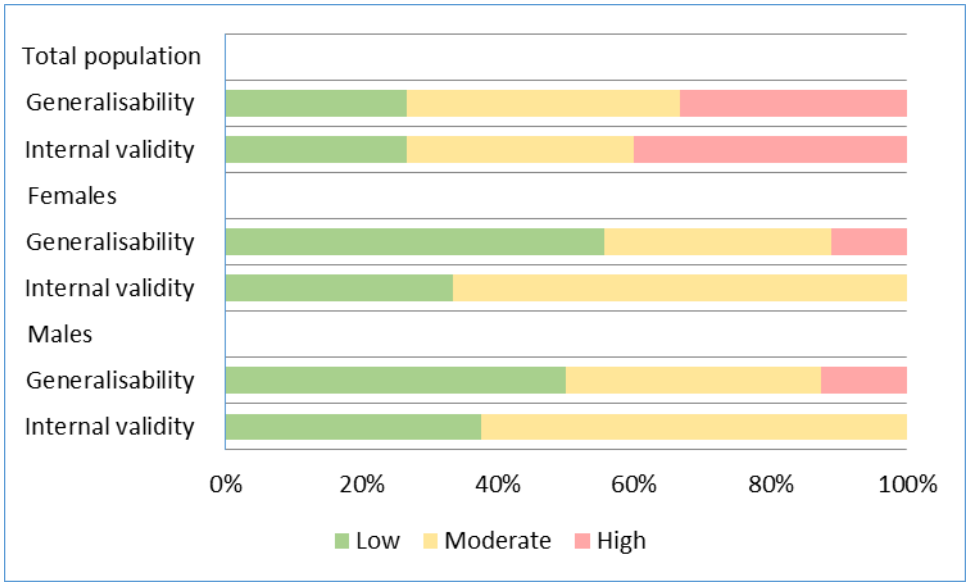


Figure 5 Risk of bias summary for studies reporting depression outcomes for adolescents who drank alcohol
Fifteen studies included results for the total population, nine studies included results for females and eight studies included results for males.

3.1.2.1 Combined gender

Alcohol consumption as a continuous variable

Twelve studies looked at predicting the development of depressive symptoms as a consequence of drinking alcohol, up to 12 years earlier in adolescents. These studies enrolled school-aged adolescents from Australia, Canada, Finland, Norway, the United Kingdom and the United States and are therefore likely to be applicable to the Australian setting. The amount of alcohol consumed and/or the frequency of consumption were quantified and used these measures or a composite of both as a continuous variable in regression analysis models. The presence of depressive symptoms

was assessed using self-reported questionnaires. The scores from these questionnaires were either used as a continuous variable, or they were dichotomised for the presence or absence of the condition. The correlation coefficients and the related p-values from regression analysis were then reported.

Two studies reported on the likelihood of developing depressive symptoms as the result of increasing alcohol consumption at an earlier age. A large Canadian study with good internal validity by Hooshmand et al. (2012) enrolled over 4,000 school students aged 14 years at baseline and assessed their alcohol intake and depressive symptoms every year for three years. They constructed continuous variables for alcohol quantity and depressive symptoms and calculated the Pearson correlation coefficients. The authors found a significant positive correlation between alcohol quantity and depressive symptoms for all comparisons (Table 6). A small American study by Mason et al. (2008) that had poor internal validity included only 429 school students initially assessed at age 16 years and re-assessed at ages 18 years and 22 years. The authors reported the beta coefficient between having depressive symptoms at ages 16 and 18 years, and/or a major depressive episode (MDD) by age 22 years and the amount of alcohol consumed at ages 16 and 18 years. All comparisons showed a positive association, although the association between alcohol consumption quantity at age 16 years and having depressive symptoms by age 18 failed to reach statistical significance. This is probably due to the small study being underpowered to detect a significant difference.

All comparisons between alcohol intake quantity and depressive symptoms at the same age, except at age 17 years, showed a significant positive association (GRADE ⊕⊕⊖⊖).

All observations between depressive symptoms up to age 18 and MDD at age 22 and earlier alcohol intake showed a positive association, but the association between alcohol intake at age 16 years and depressive symptoms at age 18 years from a small study with a high risk of bias failed to reach statistical significance (GRADE ⊕⊕⊖⊖).

Table 6 A grid representing the results from all studies reporting on the correlation between alcohol consumption quantity at a specific age and depressive symptoms evaluated at the same or a later age

		Alcohol consumption quantity at:			
		Age 14 years	**Age 15 years**	**Age 16 years**	**Age 17 years**
Depressive symptoms at age:	**14 years**	*r*=0.09, p<0.05 Hooshmand et al. (2012), N=4,412			
	15 years	*r*=0.10, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.16, p<0.05 Hooshmand et al. (2012), N=4,412		
	16 years	*r*=0.07, p<0.001 Hooshmand et al. (2012), N=4,412	*r*=0.12, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412 β=0.11, p<0.01 Mason et al. (2008) N=429	
	17 years	*r*=0.14, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.08, p<0.001 Hooshmand et al. (2012), N=4,412	*r*=0.04 Hooshmand et al. (2012), N=4,412
	18 years			β=0.10 Mason et al. (2008) N=429	
	22 years			β=0.21, p<0.01	

		Alcohol consumption quantity at:			
		Age 14 years	**Age 15 years**	**Age 16 years**	**Age 17 years**
				Mason et al. (2008) N=429	

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant correlations. Hooshmand et al. (2012) calculated the Pearson correlation between continuous alcohol quantity and depressive symptoms variables. Mason et al. (2008) used SEM regression analysis with alcohol quantity as an ordinal variable and depressed mood as a continuous variable.

Both Hooshmand et al. (2012) and Mason et al. (2008) also reported on the effect of increasing frequency of drinking alcohol (irrespective of the amount of alcohol consumed per session) on the later development of depressive symptoms. Hooshmand et al. (2012) calculated the Pearson correlation coefficients for alcohol frequency and depressive symptoms. The authors found a significant positive correlation between alcohol drinking frequency and depressive symptoms for all comparisons (Table 7). Again the small study by Mason et al. (2008) found positive associations between drinking frequency and depressive symptoms, but the association between drinking frequency at age 16 and MDD at age 22 years failed to reach statistical significance.

Two additional studies reported on this comparison (Table 7). An Australian study with poor internal validity found a negative association between drinking frequency at ages 11 or 14 years and depressive symptoms at ages 14 and 16 years, respectively, but this was not statistically significant even though the study had enrolled 927 Victorian school students (Scholes-Balog et al. 2015). However, the associations between drinking frequency and depressive symptoms at the same age showed a positive correlation, with the association at age 16 being statistically significant. The other study had a low risk of bias and enrolled 620 Mexican youths living in California and found a significant positive association between drinking frequency at age 14 years and depressive symptoms at age 16 years (Parrish et al. 2016). However, after adjustment for gender and generational status and delinquency, the association was no longer statistically significant.

All comparisons between drinking frequency and depressive symptoms at the same age showed a positive association but the comparisons at age 11 and 16 years in the study by Scholes-Balog et al. (2015), which had a high risk of bias failed to reach statistical significance (GRADE ⊕⊖⊖⊖).

The observations between depressive symptoms up to age 18 and MDD at age 22 and earlier alcohol intake showed a positive association in two studies, but the association between drinking frequency at age 14 years and depressive symptoms at age 16 years reported by the small study by Parrish et al. (2016), which had a low risk of bias failed to reach statistical significance. The third study with a high risk of bias by Scholes-Balog et al. (2015) showed a non-significant negative association between depressive symptoms and drinking frequency at an earlier age (GRADE ⊕⊖⊖⊖).

Table 7 A grid representing the results from all studies reporting on the correlation between alcohol drinking frequency at a specific age and depressive symptoms evaluated at the same or a later age

		Drinking frequency at:				
		Age 11	**Age 14**	**Age 15**	**Age 16**	**Age 17**
Depressive symptoms at:	**Age 11**	β=0.015 Scholes-Balog et al. (2015), N=927				
	Age 14	β=−0.051 Scholes-Balog et al. (2015), N=927	*r*=0.22, p<0.05 Hooshmand et al. (2012), N=4,412 β=0.143, p<0.001 Scholes-Balog et al. (2015), N=927			
	Age 15		*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.17, p<0.05 Hooshmand et al. (2012), N=4,412		
	Age 16		*r*=0.10, p<0.05 Hooshmand et al. (2012), N=4,412 β(adj)=0.04 Parrish et al. (2016), N=620 β=−0.035 Scholes-Balog et al. (2015), N=927	*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412 β=0.19, p<0.01 Mason et al. (2008), N=429 β=0.049 Scholes-Balog et al. (2015), N=927	
	Age 17		*r*=0.11, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.10, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.09, p<0.05 Hooshmand et al. (2012), N=4,412	*r*=0.12, p<0.05 Hooshmand et al. (2012), N=4,412
	Age 18				β=0.22, p<0.001 Mason et al. (2008), N=429	
	Age 22				β=0.08 Mason et al. (2008), N=429	

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant correlations. Hooshmand et al. (2012) calculated the Pearson correlation between continuous alcohol frequency and depressive symptoms variables. Mason et al. (2008) used SEM regression analysis with alcohol quantity as an ordinal variable and depressed mood as a continuous variable. Parrish et al. (2016) used SEM regression analysis with drinking frequency and depressive symptoms as continuous variables. Adjusted for gender and generational status and delinquency. Scholes-Balog et al. (2015) used SEM cross-lagged path analysis with drinking frequency as a binary variable and depressed mood as a continuous variable;

Three studies reported on the correlation of alcohol consumption as a composite of both quantity and drinking frequency with later development of depressive symptoms in adolescents or young adults. One small study with poor internal validity by Mackie et al. (2011), enrolling 393 youths aged 14 years, reported a significant positive correlation between adolescent alcohol use at age 14 years and 15 years, and depression at the same time or 6 months later (Figure 6). However, by 12 month the correlation between alcohol consumption and depression became insignificant. SEM regression analysis of the causal relationship between alcohol use and depression found that high initial levels in Q×F alcohol use did not predict change in depression (Q×F intercept-depression slope β=0.03, p=0.45). Two larger studies reported a significant positive correlation between drinking at age 16 years and the development of depressive symptoms 2 and 12 years later (Table 8). The study by Patwardham et al. (2017) had good internal validity and enrolled 6,963 adolescents aged 16 years to

investigate the correlation between drinking at age 16 years and the diagnosed depression 12 years later. The Spearman's rank-order correlation was significantly positive, and the SEM beta coefficient also reported a significant positive association (Table 8). The study by Mason & Spoth (2011), with poor internal validity enrolled 1,521 16-year olds and found a positive correlation between their drinking habits and the development of depressive symptoms at age 18 years.

All comparisons between alcohol consumption and depressive symptoms at the same age showed a significant positive association. The study by Mackie et al. (2011) with a high risk of bias showed that this association could last for up to 6 months (GRADE ⊕⊖⊖⊖).

The observations between depression and earlier alcohol consumption showed a positive association, which was statistically significant in two out of three comparisons (GRADE ⊕⊖⊖⊖).

Table 8 A grid representing the results from all studies reporting on the correlation between alcohol consumption (quantity x frequency) at a specific age and depressive symptoms evaluated at the same or a later age

		Alcohol consumption quantity × frequency at:		
		Age 14	**Age 15**	**Age 16**
Depressive symptoms at:	**Age 14**	*r*=0.20, p<0.001 Mackie et al. 2011 (N=393)		
	Age 15	*r*=0.08 Mackie et al. 2011 (N=393)	*r*=0.14, p<0.05 Mackie et al. 2011 (N=393)	
	Age 16			β=0.24, p<0.05 Mason & Spoth 2011 (N=151)
	Age 18			β=0.27, p<0.05 Mason & Spoth 2011 (N=151)
	Age 28			rho=0.072, p<0.001 β=0.10, p<0.001 Patwardham et al. 2017 (N=6,963)

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant correlations. Mackie et al. (2011) calculated the Pearson correlation between continuous alcohol frequency and depressive symptoms variables. Mason & Spoth (2011) used SEM regression analysis with a summed alcohol quantity-frequency index and depressed mood as continuous variables. Patwardham et al. (2017) calculated the Spearman's rank-order correlation between a continuous alcohol consumption variable and a binary depressive symptoms variable.

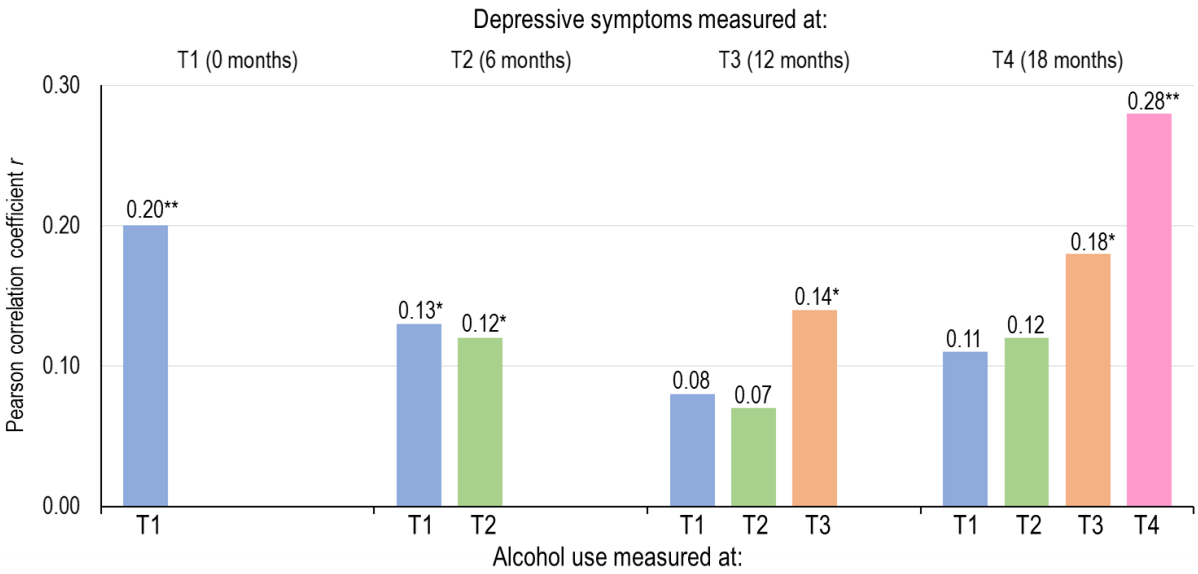


Figure 6 Bar graph depicting the Pearson correlation coefficient between alcohol consumption Q×F measured at age 14 (T1), then 6 (T2), 12 (T3) and 18 (T4) months later and depressive symptoms at T1, T2, T3 and T4

The x-axis represents the wave at which alcohol use was assessed. Alcohol use was a composite of quantity and frequency. The blue bars represent alcohol measures taken from T1 (age 14 years). The green bars represent alcohol measures taken 6 months later. The orange bar represents alcohol measures taken at 12 months and the pink bar represents alcohol measures taken at 18 months. The time-point from which the depressive symptom measures were taken is shown at the top of the graph. The asterisks indicates statistical significance (* p<0.05 and ** p<0.001). (Mackie et al. 2011)

One study by Needham (2007) enrolled 10,828 school children with a mean age of 15 years and measured baseline HED frequency over the past 12 months and depressive symptoms six years later. This study had moderate internal validity and used dual latent growth models to report the unstandardized coefficients for the intercept of HED with the slope of depressive symptoms. Initial levels of HED was positively correlated with initial levels of depressive symptoms (i.e. those who participated in HED were had higher levels of depressive symptoms on average than those who did not participate in HED). The intercept of HED also predicted the rate of change in depressive symptoms. The authors reported a negative association with adolescents who drank more heavily at age 15 years, having a significantly faster rate of decline in symptoms of depression across the transition to adulthood (age 21 years) (B=−0.20, p<0.001) (GRADE ⨁⨁⊖⊖). That is, those with higher levels of HED (and depressive symptoms) at baseline had a faster reduction in depressive symptoms, (possibly due to regression to the mean), than those with lower baseline HED (and depressive symptom levels).

Alcohol consumption as a categorical variable

Two studies with moderate internal validity reported on the correlation between any alcohol consumption (compared with no alcohol consumption) in adolescents aged 11−14 years and later development of depressive symptoms. These studies dichotomised alcohol consumption into two groups: those who drank more than a few sips of alcohol regardless of quantity or frequency, and those who did not. The study by Birkley et al. (2015) found a significant positive phi correlation between those who drank alcohol at age 11 or 12 years and those who had depressive symptoms at age 11 and/or 12 years (Table 9); a phi correlation is similar to the Pearson correlation coefficient in its interpretation. The second study by McCarty et al. (2012) was smaller, enrolling only 512 adolescents aged 12 years. This study found mostly significant positive associations between drinking and depressive symptoms at ages 12, 13, 14 and 15 years. The association between drinking at age 13 years and depressive symptoms at age 14 or 15 years was not significant. This is likely due to the small study being underpowered to detect all outcomes.

These results suggest there is *limited evidence of an association* between consuming alcohol and having depressive symptoms at the same age (GRADE ⊕⊖⊖⊖).

These results suggest there is *limited evidence of an association* between consuming alcohol and having depressive symptoms at a later time-point (GRADE ⊕⊖⊖⊖).

Table 9 A grid representing the results from all studies reporting on the correlation between any alcohol consumption at a specific age and depressive symptoms evaluated at the same or a later age

		Alcohol consumption at:				
		Age 11	**Age 12**	**Age 13**	**Age 14**	**Age 15**
Depressive symptoms at:	**Age 11**	phi=0.13, p<0.05 Birkley et al. 2015 (N=800)				
	Age 12	phi=0.14, p<0.05 Birkley et al. 2015 (N=800)	phi=0.21, p<0.001 Birkley et al. 2015 (N=800) β=0.23, p<0.01 McCarty et al. 2012 (N=512)			
	Age 13		β=0.13, p<0.01 McCarty et al. 2012 (N=512)	β=0.19, p<0.01 McCarty et al. 2012 (N=512)		
	Age 14		β=0.16, p<0.01 McCarty et al. 2012 (N=512)	β=0.08 McCarty et al. 2012 (N=512)	β=0.18, p<0.01 McCarty et al. 2012 (N=512)	
	Age 15		β=0.17, p<0.01 McCarty et al. 2012 (N=512)	β=0.02 McCarty et al. 2012 (N=512)	β=0.17, p<0.01 McCarty et al. 2012 (N=512)	β=0.15, p<0.01 McCarty et al. 2012 (N=512)

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant correlations. Birkley et al. (2015) calculated phi correlation coefficients and SEM path analysis between a binary variable for alcohol consumption and a continuous variable for depressive symptoms. McCarty et al. (2012) used SEM path analysis with alcohol consumption as a binary variable and depressive symptoms as a continuous variable.

A Norwegian study with poor internal validity by Skogan et al. (2016) reported on the association between weekly alcohol consumption at age 13−18 years compared with either stable (consistently less than weekly) or no alcohol consumption over the 5 year follow-up period (Figure 7). The weekly alcohol consumption trajectories were a composite of the four-level drinking frequency variable at ages 13, 15, 16 and 18 years. Adolescents who were weekly drinkers by age 13 years had higher depressive symptoms on average at ages 15, 16 and/or 18 years than those who consistently drank less. Similarly, adolescents who drank less than weekly at age 13 years but had started to drink weekly by age 18 had a positive association with depressive symptoms, but this only reached statistical significance for depressive symptoms at age 18 years. The positive association between drinking frequency and depressive symptoms for adolescents who started drinking after age 13 years did not reach statistical significance for any comparison (GRADE ⊕⊖⊖⊖).

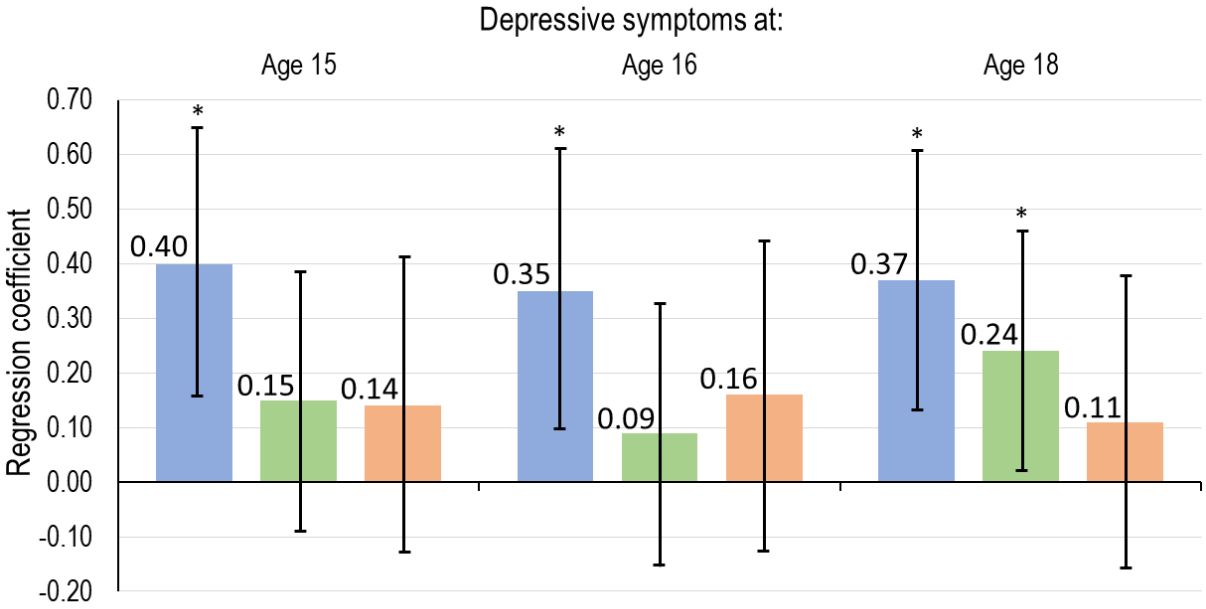


Figure 7 Bar graph depicting the linear regression beta coefficient (95% CI) for the association between alcohol consumption trajectories from age 13 years and depressive symptoms 1−3 years later

The ages shown on the x-axis represent the age at which depressive symptoms were assessed. Alcohol consumption trajectories were a composite of the four-level drinking frequency variable at ages 13, 15, 16 and 18 years. The blue bars represent adolescents who were weekly drinkers at age 13. The green bars represent adolescents who were less than weekly drinkers at age 13 years but had increased consumption to weekly by age 18 years. The orange bars represent adolescents who were non-drinkers at age 13 years but started drinking weekly by age 18 years. The reference groups were adolescents who were less than weekly drinkers or non-drinkers at age 13 years and did not greatly increase their level of alcohol consumption up to age 18 years. The 95% CIs are also shown, the asterisk indicates statistical significance. (Skogen et al. 2016).

HED or drinking to intoxication in adolescents

Six studies, including one conducted in Australia, reported on the correlation between HED or drinking to intoxication and the later development of depressive symptoms in adolescents. Five studies (one with good and four with poor internal validity) reported significant positive correlations, and one study (with moderate internal validity) reported a significant negative correlation. The mean scores from the self-reported depression measures were standardised with or without log or square-root transformations to correct for skewness and used as a continuous variable in regression analysis in all studies.

Four studies dichotomised or categorised the frequency of HED and the results are summarised in Table 10. The Australian study, by Chan et al. (2013), enrolled 969 Victorian high school students aged 14 years and reported if they had undertaken any HED (defined as ≥5 drinks/session) in the last 2 weeks. HED was dichotomised into yes or no and the mean depressed mood score were used to calculate the Spearman's rank-order correlation. The authors found a significant positive correlation between HED at age 13 or 14 years and depressive symptoms 1 or 2 years later. The study by Skogan et al. (2016) categorised 1,102 adolescents based on drinking to intoxication at ages 13, 15, 16 and 18, this was used with standardised mean depression scores in linear regression analysis. The authors found a significant positive association between drinking to intoxication at age 13 and depressive symptoms at ages 15 and 18 years, but not at age 16 years. The small study by Mason & Spoth (2011) (N=151) also reported on the correlation between HED (defined as ≥3 drinks in a row in the past month) at age 16 and depressed mood at age 18. The number of HED occasions were categorized into (0) = none, (1) = one occasion and (2) = two or more occasions, and along with the mean depressed mood scores were used in regression analysis. The authors found a significant

positive correlation between HED and depressed mood. Another small study by Mason et al. (2008), enrolled 429 adolescents and assessed the frequency of HED (defined as ≥3 drinks in a row in the past month) at age 16 years as a categorical variable and their mean depressed mood score at age 18 years as a continuous variable were used in SEM regression analysis. A significant positive association between HED at age 16 years and a depressed mood at age 18 years was reported.

Two large studies used HED frequency as a continuous variable in regression analysis and their results are also summarised in Table 10. Gustafson(2012) enrolled 3,194 high school students with a mean age of 15 years. HED frequency was defined as the number of days ≥5 drinks were consumed in a row in the last 12 months and along with the mean depressive symptoms score, also as a continuous variable, was used to calculate the Pearson correlation coefficient. The authors found a significant positive correlation between HED at age 15 years and depressive symptoms at age 15 years and at 21 years. Although there was a positive correlation between HED at age 15 years and a diagnosis of depression at age 27 years, the correlation was not statistically significant. Cisler et al. (2012) enrolled 3,614 adolescents with a mean age of 14 years and defined HED frequency as the number of times ≥5 alcoholic drinks were consumed in a single day in the last 30 days. Using multiple linear regression analyses, the authors found a non-significant positive correlation with depressive symptoms one year later and a significant negative correlation 2-years later at mean age of 17 years.

The association between alcohol consumption and depressive symptoms at the same age were reported in four studies with a high risk of bias. One study showed a significant positive association at ages 13, 14 and 15 years. One study reported positive association at age 15. Two studies showed a positive association at age 16 years but only one reached statistical significance. (GRADE ⨁⊖⊖⊖).

The observations between depression and earlier alcohol consumption showed a positive association in all studies but one. The moderate risk study by Cisler et al. (2012) showed no association between HED at age 14 and depressive symptoms at age 15 and a significant negative association one year later at age 16 years. Of 11 comparisons from the other five studies only 2 did not reach statistical significance. One of these came from the only study with a low risk of bias (Gustafson2012). (GRADE ⨁⊖⊖⊖).

Table 10 A grid representing the results from all studies reporting on the correlation between HED or drinking to intoxication as an adolescent, and depressive symptoms evaluated at the same or a later age

		HED at:			
		Age 13	**Age 14**	**Age 15**	**Age 16**
Depressive symptoms at:	**Age 13**	rho=0.20, p<0.001 Chan et al. 2013 (N=969)			
	Age 14	rho=0.15, p<0.001 Chan et al. 2013 (N=969)	rho=0.21, p<0.001 Chan et al. 2013 (N=969)		
	Age 15	rho=0.09, p<0.01 Chan et al. 2013 (N=969) β=0.30, p<0.05 Skogan et al. 2016 (N=1,102)	rho=0.08, p<0.05 Chan et al. 2013 (N=969) β=0.01 Cisler et al. 2012 (N=2,511)	rho=0.13, p<0.05 Chan et al. 2013 (N=969) *r*=0.141, p<0.01 Gustafson2012 (N=3,194)	
	Age 16	β=0.316 Skogan et al. 2016 (N=1,102)			β=0.11 Mason et al. 2008 (N=429) β=0.20, p<0.05 Mason & Spoth 2011 (N=1,521)
	Age 17		β=−0.06, p<0.05 Cisler et al. 2012 (N=1,653)		
	Age 18	β=0.27, p<0.05 Skogan et al. 2016 (N=1,102)			β=0.14, p<0.05 Mason et al. 2008 (N=429) β=0.27, p<0.05 Mason & Spoth 2011 (N=1,521)
	Age 21			*r*=0.069, p<0.10 Gustafson2012 (N=3,194)	
	Age 22				β=0.13, p<0.05 Mason et al. 2008 (N=429)
	Age 27			*r*=0.029 Gustafson2012 (N=3,194)	

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant positive correlations and the grey shading represents significant negative correlations. Chan et al. (2013) calculated Spearman's rank-order correlation with HED as an ordinal variable and depressive symptoms scores as a continuous variable. Cisler et al. (2012) used multiple linear regression analysis with HED frequency and total depressive symptom scores as continuous variables. Gustafson(2012) calculated Pearson correlation coefficients with HED frequency and depressive symptoms scores as continuous variables. Mason et al. (2008) used SEM regression analysis with HED frequency as an ordinal variable and depressed mood as a continuous variable. Mason & Spoth (2011) used SEM regression analysis with HED frequency as an ordinal variable and depressed mood as a continuous variable. Skogan et al. (2016) used linear regression analysis with drinking to intoxication as a binary variable and the mean depression score as a continuous variable.

Heavy or harmful drinking in adolescents

Two studies reported on the correlation between heavy or harmful drinking and the later development of depressive symptoms in adolescents (Table 11). The study by Skogan et al. (2016), with poor internal validity, categorised 1,102 adolescents based on weekly drinking at ages 13, 15, 16 and 18. This was used with standardised mean depression scores in linear regression analysis. The

authors found a significant positive association between high alcohol consumption at age 13 and depressive symptoms at ages 15, 16 and 18 years.

Pesola et al. (2015) had moderate internal validity but did not clearly define harmful drinking. It was determined by frequency of drinking alcohol, largest number of drinks in a single day and whether the adolescent had ever been drunk. The authors reported that harmful drinking among 4,863 14-year olds was significantly negatively associated with depressive symptoms at age 16 years. Although they reported a positive Spearman's correlation between harmful drinking at age 14 years and depressed mood 2 years later (rho=0.33, p<0.001) and a total unadjusted effect of harmful drinking at age 14 years predicted greater depressed mood 2 years later (β=0.092, p < .001), 95% of this correlation could be accounted for by affiliation with deviant peers. Thus, the direct effect, after accounting for other possible confounders showed a negative correlation (β_{adj}=−0.065, p<0.001) and may reflect drinking among those adolescents who engage in alcohol use to socialize.

Pesola et al. (2015) found a significant positive association between harmful drinking and depressed mood at age 14 years. (GRADE ⊕⊕⊖⊖).

All observations between depressive symptoms and earlier heavy or harmful drinking showed a significant positive association. (GRADE ⊕⊖⊖⊖).

Table 11 A grid representing the results from all studies reporting on the correlation between heavy or harmful drinking as an adolescent, and depressive symptoms evaluated at the same or a later age

		Heavy or harmful drinking at:	
		Age 13	**Age 14**
Depressive symptoms at:	**Age 14**		rho=0.13, p<0.05 Pesola et al. 2015 (N=1,883)
	Age 15	β=0.40, p<0.05 Skogan et al. 2016 (N=1,102)	
	Age 16	β=0.35, p<0.05 Skogan et al. 2016 (N=1,102)	rho=0.33, p<0.001 Pesola et al. 2015 (N=1,883)
	Age 18	β=0.37, p<0.05 Skogan et al. 2016 (N=1,102)	

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant positive correlations. Pesola et al. (2015) calculated the Spearman's rank-order correlation and used SEM regression analysis with an ordinal harmful drinking variable and a continuous depressed mood variable. Skogan et al. (2016) used linear regression analysis with drinking to intoxication as a binary variable and the mean depression score as a continuous variable.

3.1.2.2 Female and male subgroup analysis

One Australian study with moderate internal validity looked at the likelihood of HED in adolescent and young adult females leading to depression 6 years and 15 years later (Powers et al. 2016). The women were enrolled at 18−23 years of age and HED frequency at ages 16 to 21 years was assessed retrospectively. The authors found that women who drank episodically more than once a week when they were aged 16−21 years had a 30% increase in the likelihood of having depression at age 22−27 years compared to women who did not drink episodically (Figure 8). Although the point estimate shows a 20% increase in the chance of having depression at 31−36 years, it did not reach statistical significance and the wide 95% CIs suggest that the study may have been underpowered for this outcome. Less frequent HED (once weekly or less often) at age 16−21 years did not increase the chance of having depression in either age group compared to women who did not drink episodically (GRADE ⊕⊕⊖⊖).

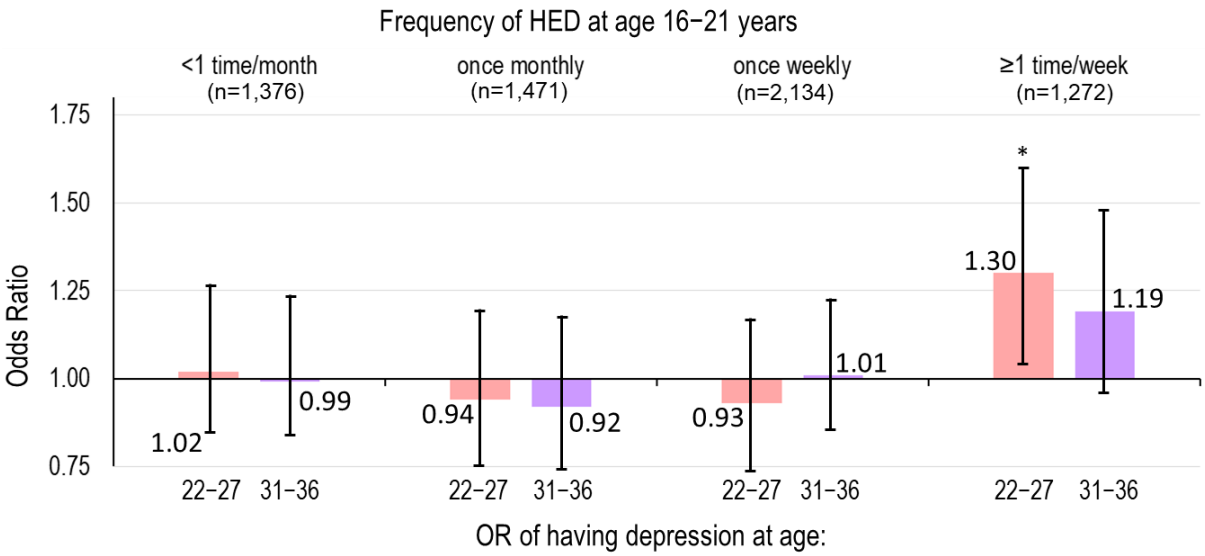


Figure 8 Bar graph depicting the OR (95% CI) for the likelihood of females having depression if participating in HED 6−15 years earlier compared with no HED

The 95% CIs are shown, the asterisk indicates statistical significance. The age of assessing depression are shown below the x-axis. The no HED group (n=1,998) was used as the reference in logistic regression analysis (Powers et al. 2016). Both depressive symptoms and HED frequency were used as categorical variables.

One study with moderate internal validity (Edwards et al, 2014) reported the odds ratios (OR) and 95%CIs for the increased likelihood of adolescents aged 16 years developing depression according to their drinking frequency 1−3 years earlier, compared with little or no alcohol consumption (Figure 9). The study did not report the cut-offs for low, medium or high drinking frequency, but defined them as none, occasional or weekly alcohol use over time between ages of 13 years to 15 years. Adolescents were categorised as having depression if they met the ICD criteria for a depressive episode. The authors found a significant increase in the likelihood of adolescents having had a depressive episode by age 16 years if they were a medium or high frequency drinker at age 14 years compared to low frequency drinkers (GRADE ⊕⊕⊖⊖).

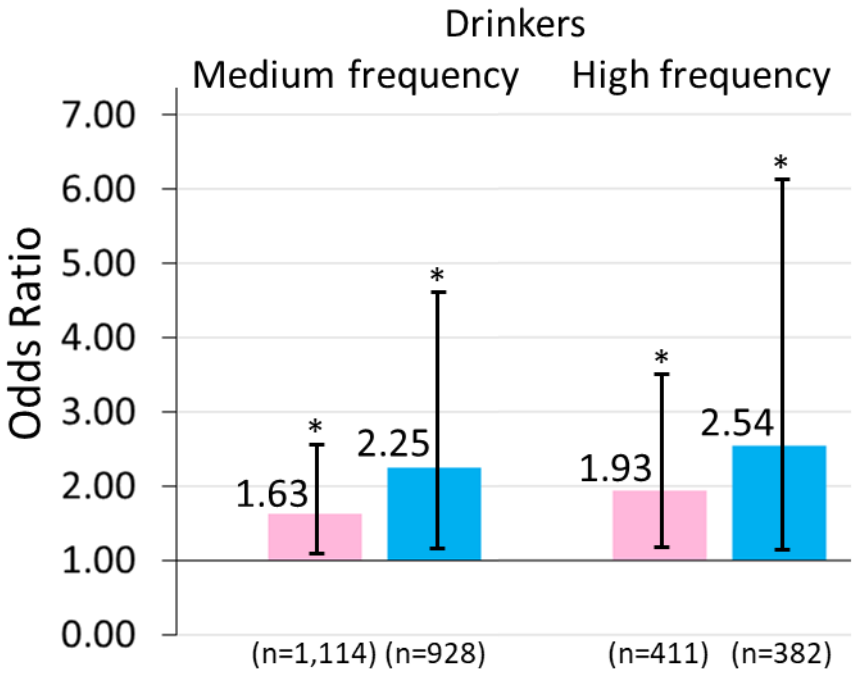


Figure 9 Bar graph depicting the OR (95% CI) for the likelihood of having had a depressive episode at age 16 years if drinking moderately or heavily 1−3 years earlier compared with drinking little or no alcohol

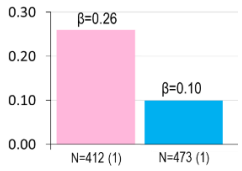
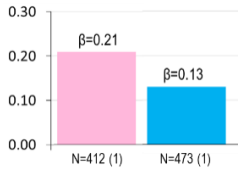
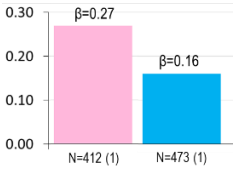
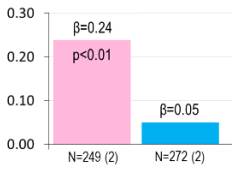
The pink bars represent the OR point estimates for females (N=2,414) and the blue bars represents those for males (N=1,878) at different drinking levels from Edwards et al. (2014). The 95% CIs are also shown, the asterisk indicates statistical significance. The low alcohol consumption group (n=2,105 boys and n=2,105 girls) was used as the reference group in logistic regression analysis. Both drinking frequency over time (ages 13–15) and depressive episodes were categorical variables.

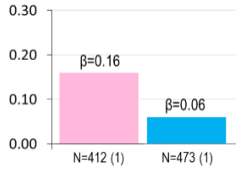
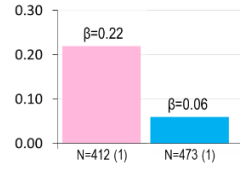
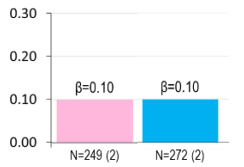
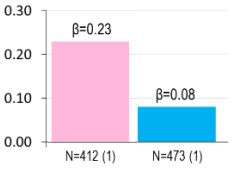
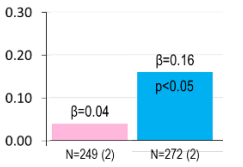
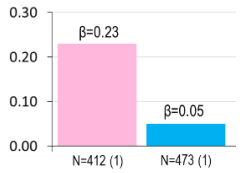
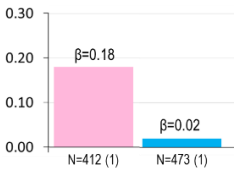
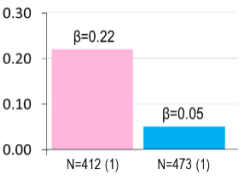
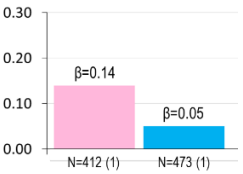
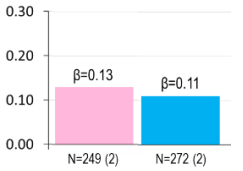
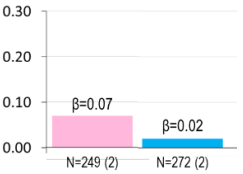
Two small studies with moderate internal validity from the United States reported on the correlation between alcohol drinking frequency during adolescence and depressive symptoms up to 3 years later for males and females (Table 12). Fleming et al. (2008) reported alcohol drinking frequency as a 6-catergory variable: (0) no use in the previous year, (1) some use in the past year but none in the past month, (2) once or twice in the past month, (3) three to five times in the past month, (4) 6 to 19 times in the past month, and (5) 20 or more times in the past month. Depressive symptoms were reported as the score with a range from 0 to 3. Using multivariate latent growth trajectory models, the authors found no significant associations for any of the comparisons shown in Table 12 for either males or females. However, the authors concluded that although caution should be exercised in comparing correlation coefficients across groups, most of the correlations are larger in magnitude for girls than for boys.

Wymbs et al. (2014) assessed alcohol drinking frequency from 0 (never used) to 7 (used more than once per day). Together with depressive symptoms scores these variables were used in structural equation modelling and the authors reported that alcohol use failed to predict depressive symptoms in the following 4 years. The larger effect for girls seen in the study by Fleming et al. (2008) was not consistent in this study. There was a significant association between alcohol use at age 14 years and depressive symptoms at the same age in girls but not boys. However, by ages 15 and 18 years the association was no longer significant and did not differ between girls and boys. Conversely, alcohol use at age 15 years was significantly associated with depressive symptoms at the same age in boys but not girls, and again by age 16 the association became nonsignificant.

For both male and female adolescents, it was considered that there was *no evidence of an association* between alcohol drinking frequency and (GRADE ⨁⊖⊖⊖).

Table 12 A grid representing the results from both studies reporting on the association between alcohol drinking frequency at ages 13, 14 or 15 years and depressive symptoms 1−4 years later

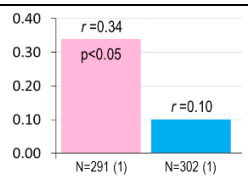
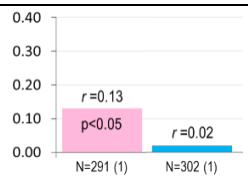
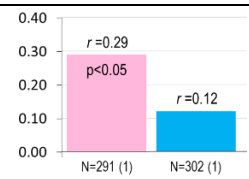
		Alcohol consumption frequency at:			
		Age 13	**Age 14**	**Age 15**	**Age 16**
Depressive symptoms at:	**Age 13**				
	Age 14		 		

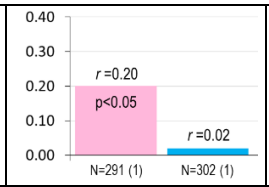
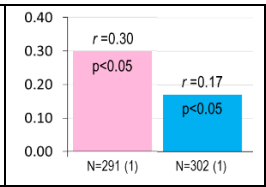
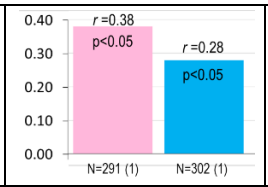
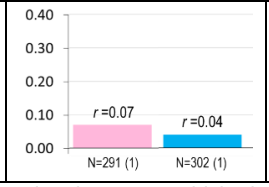
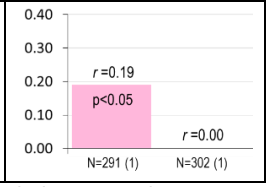
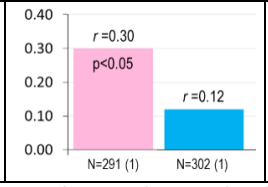
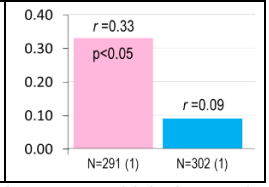
		Alcohol consumption frequency at:			
		Age 13	**Age 14**	**Age 15**	**Age 16**
	Age 15		 	 	
	Age 16				
	Age 18				

The pink bars represent the results for females and the blue bars represents results for males. The ages shown on the x-axis represent the age at which the alcohol drinking frequency was assessed followed by the age at which depressive symptoms were assessed. (1) Fleming et al. (2008) determined the β coefficients using Latent growth curve analysis with alcohol drinking frequency as a categorical variable and depressive symptoms as a continuous variable. (2) Wymbs et al. (2014) reported SEM correlation coefficients using drinking frequency and depressive symptoms as continuous variables.

One study with good internal validity reported on the correlation between alcohol consumption quantity as an adolescent, and depressive symptoms evaluated at a later age (Table 13). The study by Danzo et al. (2017) found all bivariate Pearson correlations for girls (except alcohol consumption at age 12 years and depressive symptoms at age 15 years) were statistically significant, but only boys who drank at age 13 or age 14 had a significant positive correlation with the development of depressive symptoms at age 14. (GRADE ⊕⊕⊖⊖).

Table 13 A grid with bar graphs representing the results from two studies reporting on the correlation between alcohol consumption (quantity x frequency) at a specific age and depressive symptoms evaluated at a later age for males and females

		Alcohol consumption quantity x frequency at:			
		Age 12	**Age 13**	**Age 14**	**Age 15**
Depressive symptoms at:	**Age 12**				
	Age 13				

	Age 14				
	Age 15				

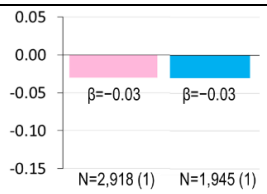
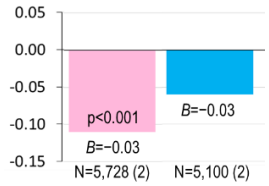
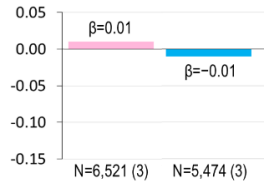
Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are graphed in the intersecting cell. Pink bars represent results for girls, and blue bars represent results for boys. Significant results are indicated by the p-value (1) Danzo et al. (2017) calculated Pearson correlation coefficients with alcohol quantity over the last month and mean depressive symptoms score as continuous variables.

Three studies reported on the correlation between HED during adolescence and depressive symptoms up to 14 years later (Table 14). A study with a good internal validity by Wilkinson et al. (2016) enrolled adolescents aged 15 years and used linear regression analysis to investigate the relationship between HED frequency and depressive symptoms up to 13 years later. Pesola et al. (2015) enrolled 5,216 adolescents aged 16 years and looked at the association between harmful drinking and depressed mood 2 years later. This study, with moderate internal validity, did not clearly define harmful drinking, but it was determined by frequency of drinking alcohol, largest number of drinks in a single day and whether the adolescent had ever been drunk. However, the authors found that the SEM β coefficient showed a negative direct effect but was not statistically significant for males or females. The difference in direct effect between males and females was also not significant (difference: β=−0.002 (−0.10, 0.10), p=1.0). Needham et al. (2007) enrolled 10,828 school children with a mean age of 15 years and measured baseline HED frequency over the past 12 months and depressive symptoms six years later. The study had moderate internal validity and used dual latent growth models and reported the unstandardized coefficients for the intercept of HED with the slope of depressive symptoms. The intercept of HED predicted the rate of change in depressive symptoms. The authors reported a negative association, with both males and females who participated in HED at age 15 years, having a significantly faster rate of decline in symptoms of depression across the transition to adulthood (age 21 years) (Table 14).

For both male and female adolescents, it was considered that there was *no reliable evidence of an association* between HED and depression (GRADE ⨁⨁⊖⊖).

Table 14 A grid with bar graphs representing the results from three studies reporting on the correlation between HED at a specific age and depressive symptoms evaluated at a later age for males and females

	HED at:	
	Age 14	**Age 15**

		HED at:	
		Age 14	**Age 15**
Depressive symptoms at:	**Age 16**		
	Age 21		
	Age 28		

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The pink shading represents correlations for females and the blue shading represents correlations for males. Significant results are indicated by the p-value. (1) Pesola et al. (2015) used SEM regression analysis with an ordinal harmful drinking variable and a continuous depressed mood variable, (2) Needham et al. (2007) used latent growth curve analysis with HED as a categorical variable and depressive symptoms as a continuous variable. (3) Wilkinson et al. (2016) linear regression analysis with HED as a categorical variable and depressive symptoms as a continuous variable.

One study with good internal validity reported on the association between HED during adolescence and the development of depressive symptoms. Schuler et al. (2015) included 6,070 individuals who participated in the Add Health study during at least one wave between the ages of 12 and 31 years. Multivariate time-varying effect modelling for the association between HED with elevated depressive symptoms was reported as age-varying coefficients with 95% CIs on a graph from age 12 to 31 years. The coefficient values and the 95% CIs were estimated from the graph and are tabulated in Table 15. HED was associated with elevated depressive symptoms only during adolescence for both females (until age 18.5 years) and males (until age 17 years) (GRADE ⊕⊕⊕⊖).

Table 15 Age-varying coefficients (95% CI) for HED associated with elevated depressive symptoms (values estimated from Schuler et al. 2015; Fig. 4)

Age at comparison	Females	Males
12 years	β~3.7 (95% CI 2.1, 5.3)	β~2.1 (95% CI 1.7, 4.4)
17 years	β~0.7 (95% CI 0.3, 1.1)	β~0.3 (95% CI 0.0, 0.3)
18.5 years	β~0.4 (95% CI 0.0, 0.8)	β~0.0 (95% CI −0.3, 0.3)
31 years	β~−0.9 (95% CI −1.6, −0.3)	β~−0.4 (95% CI −0.9, 0.3)

Pink cells refer to a significant association between HED and elevated depressive symptoms for females, and the blue cells for males. Age-varying coefficients derived using multivariate time-varying effect modelling (adjusting for daily smoking and marijuana use) with HED as a binary variable and depressive symptoms as a continuous variable.

3.1.3 Young adults

Summary:
Nine studies reported on the association between alcohol and depression or depressive symptoms in young adults.

Unlike adolescents, no reliable cross-sectional associations between measures of alcohol use (consumption quantity, frequency, or HED) and depression or depressive symptoms were found in the included studies in young adults.

Four studies reported on the association between HED and depressive symptoms across both genders. Two studies reported no statistically significant association between frequency of HED and depressive symptoms, one reported that those who participated in HED had a reduced number of depressive symptoms at follow-up, while the remaining reported that frequent HED drinkers had higher depressive symptoms than occasional HED drinkers. Individual studies focusing just on males or females, reported no significant association between HED and depressive symptoms.

One study reported that women who drank different amounts each day had no significant difference in the rate of MDD 1 year later, after adjusting for baseline levels. However, the confidence intervals were wide, suggesting the study was underpowered for this outcome.

Two studies reported on the association between alcohol consumption quantity and/or frequency and depressive symptoms or depression. Neither study reported significant associations (for either quantity or frequency or quantity x frequency). One larger study in males, reported that alcohol consumption was associated with fewer depressive symptoms, after adjusting for covariates such as drinking to cope.

Nine longitudinal cohort studies reported on the likelihood of developing either depressive symptoms or having a depressive episode as a consequence of alcohol intake as a young adult aged between 18 years and 25 years. Three of these studies reported depression outcomes for young women, and two reported outcomes for young men. The risk of bias for the studies reporting outcomes for the total population, and for males and females separately, are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 10. The majority of the studies had a low or moderate risk of bias for both the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and its generalisability to the broader population from which the study participants were selected.

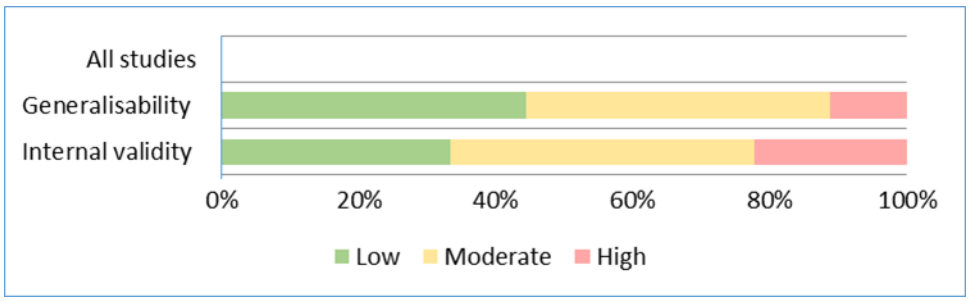


Figure 10 Risk of bias summary for studies reporting depression outcomes for young adults who drank alcohol
Eight studies included results for young adults.

3.1.3.1 Combined gender

Two small studies reported on the effect of alcohol consumption quantity and/or frequency on the development of depressive symptoms or MDD up to 4 years later (Table 16). The study by Mason et al. (2008) had poor internal validity, was conducted in the United States and included only 429 school students aged 16 years. These students were re-assessed at ages 18 years and 22 years and the authors reported the beta coefficient for the association between having a depressed mood at age 18 years or a MDD by age 22 and either the amount of alcohol consumed or the drinking frequency at age 18 years. However, this small study was underpowered and although the results indicated a positive correlation, they were not statistically significant (GRADE ⊕⊖⊖⊖). The small low risk study by Armeli et al. (2015) enrolling 522 young adults aged 19 years, reported no significant correlations between a composite score of alcohol consumption quantity and frequency and depressive symptoms 4 years later (GRADE ⊕⊕⊖⊖).

Table 16 A grid representing the results from all studies reporting on the correlation between alcohol consumption quantity and/or frequency at a specific age and depressive symptoms evaluated at a later age

		Alcohol consumption at:	
		Age 18 years	**Age 19 years**
Depressive symptoms at age:	**18 years**	Alcohol consumption quantity β=0.10 Mason et al. (2008) N=429 Alcohol consumption frequency β=0.07 Mason et al. (2008), N=429	
	22 years	Alcohol consumption quantity β=0.06 Mason et al. (2008) N=429 Alcohol consumption frequency β=0.03 Mason et al. (2008), N=429	
	23 years		Alcohol consumption quantity × frequency *b*=0.001 Armeli et al. 2015 (N=522)

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. Armelia et al. (2015) used linear regression with alcohol consumption and depressive symptoms as continuous variables and reported an unstandardized b coefficient. Mason et al. (2008) used SEM regression analysis with alcohol quantity as an ordinal variable and depressed mood as a continuous variable.

Three studies reported on the correlation between HED in young adults and depressive symptoms or a diagnosis of depression up to 6 years later (Table 17). The high risk small study by Mason et al. (2008) found a non-significant positive association between HED frequency at age 18 years and depressive symptoms at the same age and no association between HED at age 18 years and diagnosed MDD at age 22 years but the study was likely underpowered. The larger study by Piasecki et al. (2017), with moderate internal validity found a non-significant negative correlation between HED frequency and depressive symptoms. The largest study with a good internal validity by Gustafson(2012) reported a non-significant negative correlation between HED at age 21 years and depressive symptoms at the same age and a significant negative correlation between HED at age 21 years and depressive symptoms at age 27 years

The association between HED frequency and depressive symptoms at the same age did not show any significant correlations in young adults. (GRADE ⊕⊕⊖⊖).

The only significant association between HED frequency and depressive symptoms in young adults was reported by Gustafson(2012), which had a low risk of bias. (GRADE ⊕⊕⊖⊖).

Table 17 A grid representing the results from all studies reporting on the correlation between HED among young adults of legal drinking age and depressive symptoms evaluated at a later age

		HED at:				
		Age 18	**Age 21**	**Age 22**	**Age 23**	**Age 27**
Depressive symptoms at age:	**Age 18**	β=0.05 Mason et al. 2008 (N=429)				
	Age 21		*r* =−0.014 Gustafson2012 (N=3,194)			
	Age 22	β=0.00 Mason et al. 2008 (N=429)		*r* =−0.02, β=−0.026 Piasecki et al. 2017 (N=986)		
	Age 23			*r* =−0.02, β=−0.016 Piasecki et al. 2017 (N=986)	*r* =0.01, β=−0.009 Piasecki et al. 2017 (N=986)	
	Age 27		*r* =−0.045, p<0.05 Gustafson2012 (N=3,194)			*r* =−0.004 Gustafson2012 (N=3,194)

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. The green shading represents statistically significant correlations. Gustafson(2012) calculated Pearson correlation coefficients with HED frequency and depressive symptoms scores as continuous variables. Mason et al. (2008) used SEM regression analysis with HED frequency as an ordinal variable and depressed mood as a continuous variable. Piasecki et al. (2017) calculated the Pearson correlation coefficient and used SEM path regression analysis with HED frequency and depressive symptoms scores as continuous variables.

A study with moderate internal validity that was conducted in the United States by Sloan et al. (2011) categorised 7,386 young adults aged 17–25 (mean age 20.6 at baseline), according to frequency of HED into frequent HED, occasional HED and other drinkers and abstainers. The amount of alcohol consumed per group was reported in millilitres, which was converted to grams (12.5 ml = 10 g of alcohol). The depressive symptoms score at age 40 years were compared between drinking groups. The authors found that participants of frequent HED were more depressed than those of occasional HED (Table 18) but did not report on the significance of this finding. They also reported that participants of frequent HED had a similar level of depression compared to other drinkers and abstainers (GRADE ⊕⊕⊖⊖).

Table 18 Mean CES-D propensity scores for depressive symptom at age 40 years according to HED category at age 17−25 years.

Number of matched observations (N not reported)	Other drinkers and abstainers (43% of population) 1.3 g alcohol/day	Occasional HED (40% of population) 8.5 g alcohol/day	Frequent HED (17% of population) 26.4 g alcohol/day)	Difference in propensity score (95% CI)
N=2,246		30.6	34.3	3.7 (0.41, 7.1)
N=1,492	35.9		34.9	−1.0 (-5.3, 3.4)

Individuals were matched on other substance use (tobacco and illicit drugs), baseline health, educational attainment, ability and labour force status, individual motivation and long-term expectations, educational aspirations, household income, religious services attendance and rural/urban setting, as well as gender, race/ethnicity and marital status. (Sloan et al. 2011)

3.1.3.2 Female and male subgroup analysis

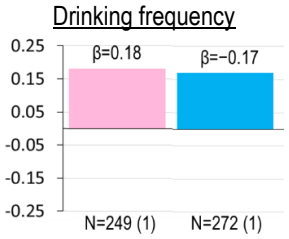
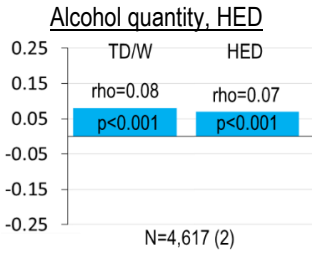
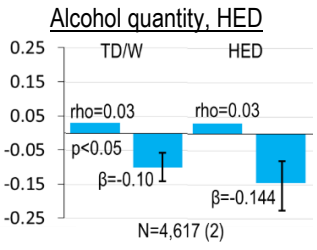
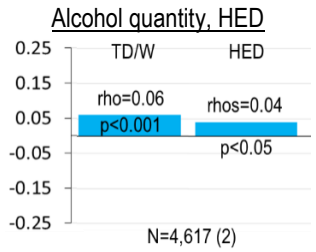
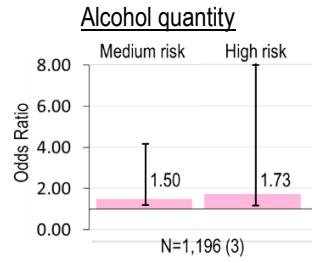
Three studies with reported on the effect of high levels of alcohol on the development of depressive symptoms or MDD in males and/or females. The study by Wymbs et al. (2014) with moderate internal validity assessed alcohol drinking frequency from 0 (never used) to 7 (used more than once per day). Together with depressive symptom scores these variables were used in structural equation modelling and the authors reported that alcohol use failed to predict depressive symptoms in the following 4 years.

Zhang et al. (2017) had good internal validity, and converted the level of alcohol consumption of young women (mean age 21 years) into grams per day, and divided them into three categories: risk level 1 for low-risk drinking (up to 20 g alcohol/day or up to 2 standard drinks/day); risk level 2 for medium-risk drinking (20–40 g alcohol/day or 2−4 standard drinks/day); and risk level 3 for high-risk drinking (over 40 g alcohol/day or >4 standard drinks/day). The presence of MDD at follow-up was assessed by a trained interviewer who administered a battery of self-reported questionnaires. The authors reported an increased likelihood of developing MDD at age 22 years if having been a medium or high risk drinker at age 21 years compared to those who were low-risk drinkers (Table 19). However, the 95% CIs are very wide indicating that the study was underpowered for this outcome (GRADE ⨁⨁⊖⊖).

The study by Grazioli et al. (2018) with moderate internal validity included an army-based cohort of 4,617 men with a mean age of 20 years also reported on the correlation between total drinks/week over the past year and depressive symptoms up to 15 months later. The authors found the Spearman's rank-order correlation between the total number of drinks/week at age 20 and depressive symptoms at ages 20 and 21 years (15 months later), as well as drinks/week at age 21 and depression at the same age, to be significantly positively correlated. In contrast, using SEM regression analysis to model HED, depressive symptoms and suicide, adjusting for drinking motives, the authors reported a significant negative association between total number of drinks/week at baseline and depressive symptoms at follow-up (β=−0.10, 95% CI −0.144, −0.053). (GRADE ⨁⨁⊖⊖).

Grazioli et al. (2018) also reported on the correlation between HED and depressive symptoms. The authors found the Spearman's rank-order correlation between males who participated in HED at age 20 and 21 and depressive symptoms at the same age to be significantly positively correlated. Although HED at age 20 and depressive symptoms at age 21 years (15 months later) was also found to be positively correlated, it did not reach statistical significance. In contrast, using SEM regression analysis to model HED, depressive symptoms and suicide, adjusting for drinking motives, the authors reported a significant negative association between HED at baseline and depressive symptoms at follow-up (β=−0.144, 95% CI −0.224, −0.065) (GRADE ⨁⨁⊖⊖). Further examination of these results indicated that it was not the alcohol consumption itself which was a risk factor, but drinking to cope.

Table 19 A grid with bar graphs representing the results from two studies reporting on the correlation between alcohol consumption at a specific age and depressive symptoms evaluated at a later age for males and females

		Alcohol consumption at:		
		Age 18	**Age 20**	**Age 21**
Depressive symptoms at age:	**Age 18**			
	Age 20			
	Age 21			
	Age 22			

TD/W = total drinks per week; HED = heavy episodic drinking

Columns characterise the age at which alcohol consumption was measured, rows characterise the age at which depressive symptoms were measured. The correlation coefficients are graphed in the intersecting cell. Pink bars represent results for girls, and blue bars represent results for boys. Significant results are indicated by the p-value or the 95% CIs not crossing 0. (1) Wymbs et al. (2014) reported SEM correlation coefficients using drinking frequency and depressive symptoms as continuous variables. (2) Grazioli et al. (2018) calculated Spearman's rank-order correlation and used SEM regression with alcohol drinking quantity and the mean score for depressive symptoms as continuous variables. (3) Zhang et al. (2017) reported the OR point estimates for MDD in female and male moderate and high risk drinkers compared to low risk drinkers.

An additional study with poor internal validity reported on the association between HED during early adulthood and the development of depressive symptoms. Mushquash et al. (2013) included 200 university women with a mean age of 20 years and looked at the short-term effect (one week) of HED on depressive symptoms. HED was defined as 4 or more drinks in a 2 hour period during the past 7 days. The authors found no association between HED and depressive symptoms using SEM cross-lagged path analysis (Table 20). This may be partially due to the small study being underpowered, but the authors concluded that HED did not influence future depressive symptoms over a 1-week period (GRADE ⊕⊖⊖⊖).

Table 20 A grid representing the results from all studies reporting on the correlation between HED among young adults of legal drinking age and depressive symptoms evaluated at a later age

		HED at:		
		T1 (week 0)	**T2 (week 1)**	**T3 (week 2)**
Depressive symptoms at:	**T1 (week 0)**	β=0.13		
	T2 (week 1)	β=0.05		
	T3 (week 2)		β=0.02	
	T4 (week 3)			β=0.02

Columns characterise the time-points at which HED was measured, rows characterise the time-points at which depressive symptoms were measured. The correlation coefficients are reported in the intersecting cell. Mushquash et al. (2013) reported SEM correlation coefficients using HED and depressive symptoms as continuous variables. None of the results were statistically significant.

3.1.4 Adults

Summary:

Both genders combined:

Three large studies reported on the effects of varying quantities of alcohol on the development of depression or depressive symptoms.

Three studies used the abstainers (with or without occasional drinkers) as the reference group. One of these studies reported that low levels of alcohol consumption (<30 g/day) was associated with a lower risk of depression than abstinence. A second study reported that anything over 1 drink per day for women, or over 1.5 for men, was associated with an increased risk of depression, with the risk increasing in a dose-dependent manner as the quantity of alcohol consumed increased.

One of these studies also provided evidence that higher levels of alcohol (>2/day for women or 3/day for men) was associated with significantly higher odds of depression.

One large study compared abstainers, drinkers exceeding guideline recommendations, HED or hazardous drinkers against guideline drinkers, non-HED or non-hazardous drinkers. Only hazardous drinkers were more likely to develop depression than non-hazardous drinkers.

This study also compared the likelihood of abstainers, special occasion drinkers, monthly drinkers and daily drinkers developing depression compared to weekly drinkers. Only daily drinkers had an increased risk of depression compared to weekly drinkers. Abstainers also showed a trend towards an increased risk of depression, but just fell short of statistical significance.

In females:

One study compared the likelihood of developing depression due to varying quantities of alcohol consumption compared with abstainers. Only one consumption sub-group had a significant difference to abstainers, although there was a trend that people who drink low levels of alcohol have less depression on average than abstainers at follow-up. This same study found no significant difference in the odds of having depression at follow-up in high consumers of alcohol vs those who were abstinent.

One study compared the likelihood of developing depression due to different frequencies of alcohol consumption compared with abstainers. Neither low frequency drinking nor high frequency drinking was associated with depression 4-years later.

In males:

Three studies compared the likelihood of developing depression or depressive symptoms due to consumption levels, frequency levels, or mean number of drinks consumed over previous week, and reported no significant difference compared with abstainers in adult males.

Five longitudinal cohort studies reported on the likelihood of developing either depressive symptoms or having a depressive episode as a consequence of alcohol intake in adults aged 18−65 years. Three studies provided data for females and two for males. The risk of bias for the studies reporting outcomes for the total population, and for males and females separately, are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 11. The majority of the studies had a moderate risk of bias for internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study, and a high risk of bias for generalisability to the broader population from which the study participants were selected.

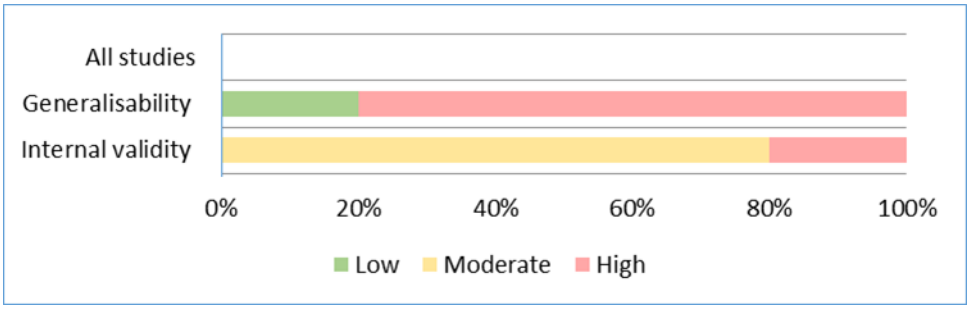


Figure 11 Risk of bias summary for studies reporting depression outcomes for adults who drank alcohol

Six studies included results for the total population, four studies included results for females and five studies included results for males.

3.1.4.1 Combined gender

The study by Bell & Britton (2015) was conducted in the United Kingdom and had moderate internal validity. The authors compared the likelihood of HEDs, hazardous drinkers, drinkers exceeding drinking guidelines and abstainers developing depression in adults aged 35–55 years over a 28-year follow-up period compared to non-HEDs, non-hazardous drinkers and drinkers who drank within the guideline recommendations. HED was defined as a maximum of ≥8(men)/≥6(women) UK units of alcohol in a single drinking session, where one UK unit equals 8 g of alcohol. Hazardous drinking was defined usually drinking ≥5 UK units/session. Drinking to exceed UK weekly drinking guidelines was considered to be ≤21/≤14 UK units for men/women per week.

There was no difference in the number of abstainers and guideline drinkers likely to develop depression over the 28-year interval (**Error! Reference source not found.**). On the other hand, drinkers who exceeded the guidelines were 14% less likely to develop depression over the 28-year period than guideline drinkers, although this did not reach statistical significance. (GRADE ⊕⊕⊖⊖).

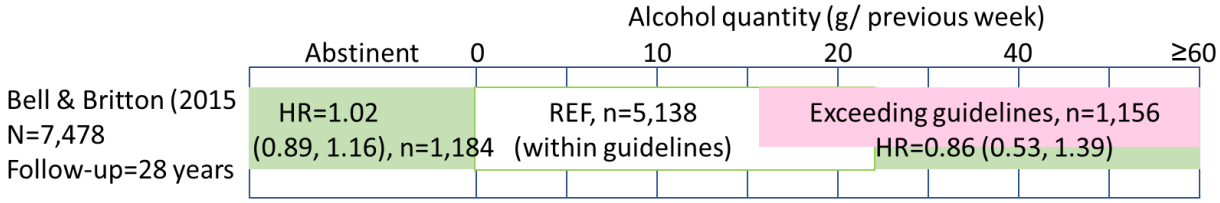


Figure 12 Graph depicting the HR (95% CI) for the likelihood of having depressed symptoms among adults according to their drinking quantity 28 years earlier compared with the indicated reference group

The green bars represent alcohol consumption (g)/day included in each drinking category for HED and hazardous drinking and drinks/week for exceeding guidelines. HRs adjusted for age, gender, socioeconomic position, marital status, smoking status, diet, physical activity and self-rated health. There were no statistically significant results.

As both HED and hazardous drinking were defined as alcohol quantity per drinking session, they were compared in **Error! Reference source not found.**. Although abstainers were 20% more likely to develop depression during the 28-year follow-up period than non-HEDs or non-hazardous drinkers, the differences did not quite reach statistical significance. There was no difference in the likelihood of developing depressive symptoms between HEDs and non-HEDs. In contrast, the comparison between hazardous and non-hazardous drinkers did reach statistical significance with hazardous drinkers 20% less likely to develop depression over the 28-year period than non-hazardous drinkers (GRADE ⊕⊕⊖⊖).

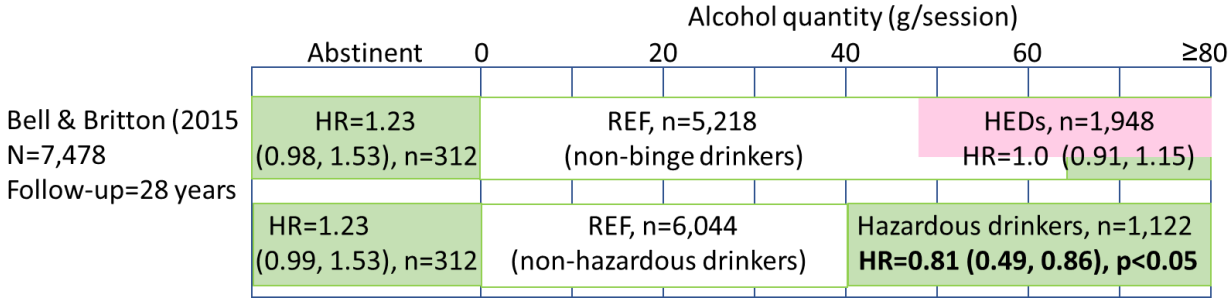


Figure 13 Graph depicting the HR (95% CI) for the likelihood of having depressed symptoms among adults according to their HED quantity 28 years earlier compared with the indicated reference group

The purple bars represent the number of drinks/session included in each drinking category for HED and hazardous drinking and drinks/week for exceeding guidelines. Statistically significant results are shown in boldface. HRs adjusted for age, gender, socioeconomic position, marital status, smoking status, diet, physical activity and self-rated health.

The study by Bell & Britton (2015) also compared the effect of drinking frequency on developing depression in adults, aged 35–55 years, over the 28-year follow-up period (**Error! Reference source not found.**). The participants were categorised as never drinkers, special occasion drinkers, monthly drinkers, weekly drinkers and daily drinkers. The authors used weekly drinkers as the reference group. There was no difference in the number of participants who developed depression over the 28-year period between, special occasion drinkers, monthly drinkers and weekly drinkers. However, abstainers were 20% more likely to develop depression over the 28-year period compared with weekly drinkers, and this almost reached statistical significance. Daily drinkers had a significant 17% increase in their likelihood of developing depression over 28-years compared to weekly drinkers (GRADE ⊕⊖⊖⊖).

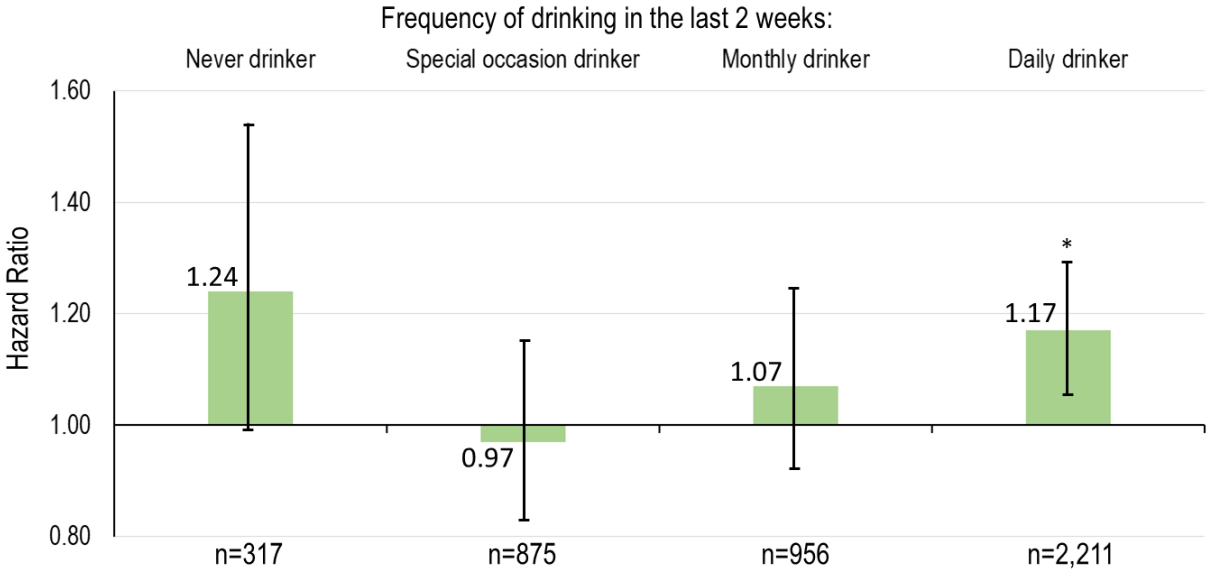


Figure 14 Bar graph depicting the HR (95% CI) for the proportion of participants likely to develop depression over a 28-year follow-up period according to drinking frequency

The weekly drinkers group was used as the reference group in regression analysis. The 95% Cis are shown, the asterisk indicates statistical significance. (Bell & Britton 2015)

Two large studies with moderate internal validity reported the OR or HR and the 95% CIs for the likelihood of adults developing depression or depressive symptoms 4–28 years after the assessment of their drinking habits according to the number of drinks/day. Two of the studies used the abstinent group as the reference group. However, their drinking categories, which were based on the baseline drinking habits of participants, were overlapping between studies and could not be combined. A Spanish study by Gea et al. (2012) divided adult university graduates with a mean age of 38 years

into four groups: abstainers (0 g/day), <10 g alcohol/day, 10−25 g alcohol/day and >25 g/day. The authors later redivided the drinkers into different subgroups (<5 g/day, 5−15 g/day and >15 g/day) after regression spline analysis. The Finnish study by Paljarvi et al. (2009) categorized the participants of working age according to quintiles of the alcohol intake distributions separately for men and women (1–37; 38–110; 111–168; 169–255; and >255 g/week for men; 1–19; 20–48; 49–78; 79–138; and >138 g/week for women).

The alcohol categories (in g/day) were graphed to show the overlapping groups (Figure 15) so that the results could be compared. Gea et al. (2012) found that participants who consumed 0.5−1.5 drinks/day were 35% less likely to develop depression during the 4−10 year period than abstainers (GRADE ⊕⊕⊖⊖). Paljarvi et al. (2009) found that the groups consuming higher levels of alcohol were at an increased risk of developing depressive symptoms compared to non-drinkers. The odds of developing depressive symptoms significantly increased (in a dose-dependent manner) from 11% greater than non-drinkers for those with a modest intake of between 1 and 2 drinks/day to 43% greater for women and men who consumed ≥2 and ≥3.5 drinks/day, respectively. The difference between the reference group and the three highest alcohol consumption groups were statistically significant. (GRADE ⊕⊕⊖⊖).

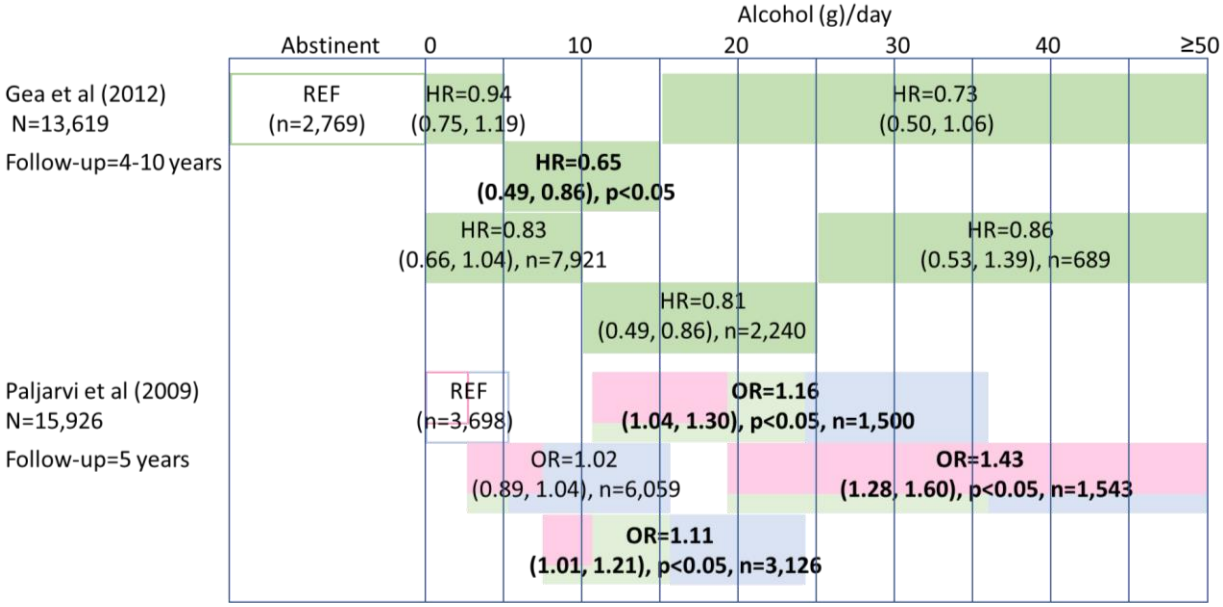


Figure 15 Graph depicting the OR, HR and the 95% CIs for the likelihood of having depressed symptoms among adults according to their drinking quantity 4−10 years earlier compared with drinking no alcohol

The green bars represent the number of g alcohol/day included in each drinking category for Gea et al. (2012). The pink and blue bars represent the number of g alcohol/day included for females and males, respectively, in each drinking category used by Paljarvi et al. (2009). The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each group (when reported) is also shown. Gea et al. (2012): HRs adjusted for age, gender, smoking, physical activity, total energy intake, baseline body mass index, adherence to the MDP, marital status, and employment status. Paljarvi et al. (2009): ORs adjusted for gender, age and BDI scores at Wave 1.

The Finnish study by Paljarvi et al. (2009), with moderate internal validity investigated the likelihood of developing depressive symptoms after 5 years, according to the number of times per year participants became intoxicated. Alcohol intoxication frequency was categorized as none (reference group), 1−5 times/year, 6 times/year, 12 times/year and ≥24 times/year (Table 21). Paljarvi et al. (2009) found that the groups who became intoxicated more frequently were at an increased risk of developing depressive symptoms compared to non-drinkers, in what appeared to be a dose-dependent manner, from 14% greater than participants who do not get drunk for those who only become intoxicated 5 times a year or less to 49% greater for those who become intoxicated at least

twice a month, respectively. However, these differences did not reach statistical significance. (GRADE ⨁⨁⊖⊖).

Table 21 OR for developing depressive symptoms according to frequency of intoxication 5 years earlier

	None (reference group)	1−5 times/year	6 times/year	12 times/year	≥24 times/year
OR (95% CI)	1.00	1.14 (1.05, 1.24)	1.22 (1.09, 1.38)	1.20 (1.08, 1.35)	1.49 (1.34, 1.65)

ORs were adjusted for gender, age and BDI scores at Wave 1 (categorized into six categories: 0, 1–4, 5–9, 10–14, 15–19, ≥20). The green shading represents statistically significant results. (Paljarvi et al. 2009)

3.1.4.2 Female and male subgroup analysis

Gea et al. (2012), with moderate internal validity, divided the participants with a mean of age 38 years into four groups: abstainers (0 g/day), <10 g alcohol/day, 10−25 g alcohol/day and >25 g/day. The authors also redivided the drinkers into different subgroups (<5 g/day, 5−15 g/day and >15 g/day) after regression spline analysis (Figure 16). The authors reported only one statistically significant outcome, they found that women who consumed 0.5−1.5 drinks/day were 40% less likely to develop depression than abstainers between 4 and 10 years later (GRADE ⨁⨁⊖⊖).

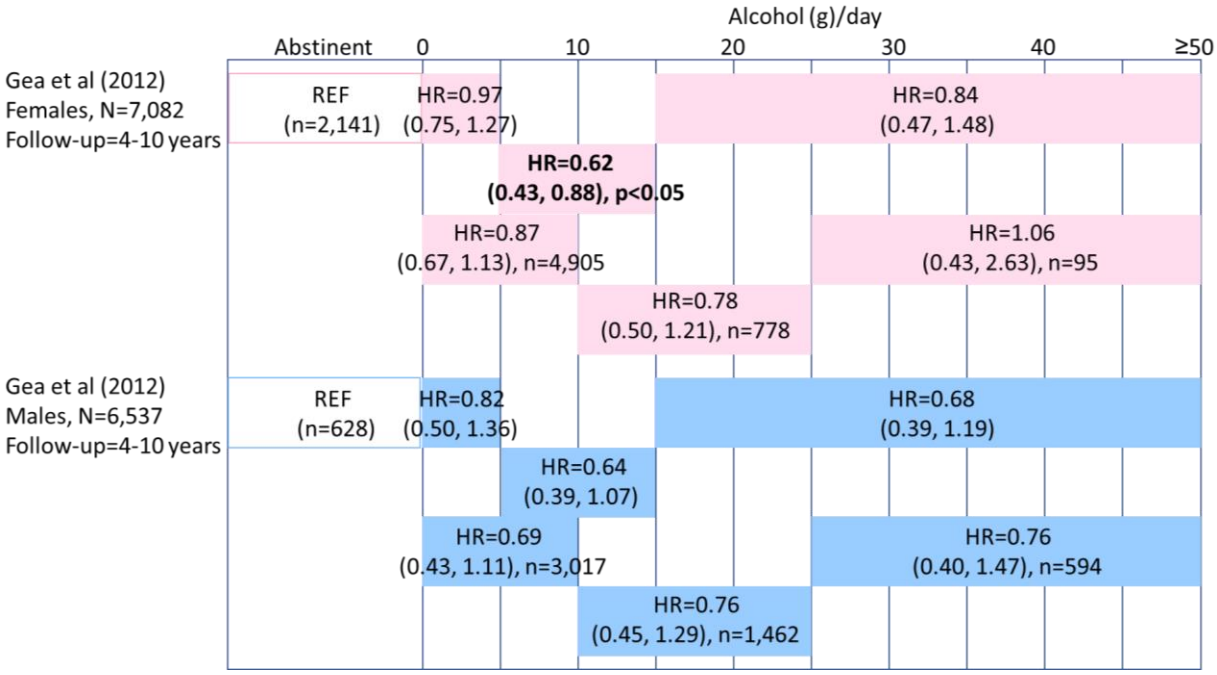


Figure 16 Graph depicting the HR, OR and the 95% CIs for the likelihood of having depressed symptoms among adult males and females according to their drinking quantity 4−10 years earlier compared with drinking no alcohol

The pink and blue bars represent the number of drinks/day included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. Gea et al. (2012): HRs adjusted for age, smoking, physical activity, total energy intake, baseline body mass index, adherence to the MDP, marital status, and employment status. Nadkarni et al. (2016): ORs adjusted for age, residence, religion, marital status, education, employment status and socioeconomic status.

Augestad et al. 2008 compared the effect of drinking frequency on developing depression in male and female adults, aged 20 – 50 years, over the following 3−12 years. The participants were categorised as abstainers, no drinking in the last 2 weeks, or as drinking 1−4, 5−10 or ≥10 times in the last 2 weeks. The authors used abstainers as the reference group.

There were no significant differences in the number of males and females who developed depression compared to abstainers over the follow-up period for any of the drinking categories (Figure 17). Even though this study enrolled 3,308 men and 3,353 women, the wide 95% Cis suggest that this study was underpowered to detect a significant difference for this outcome (GRADE ⊕⊕⊖⊖).

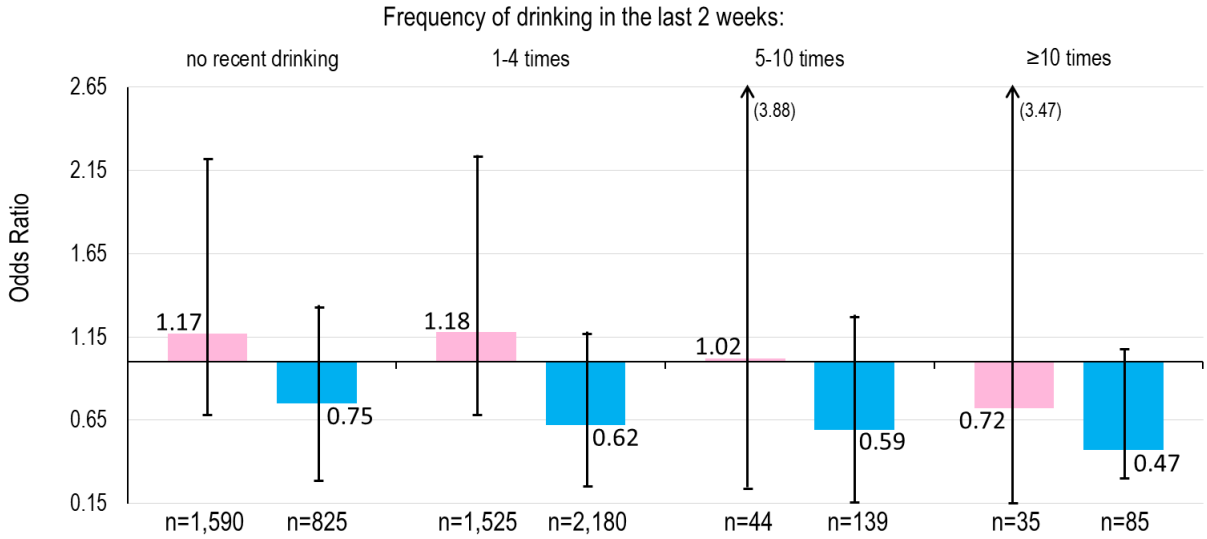


Figure 17 Bar graph depicting the OR (95% CI) for the likelihood of having depression according to drinking frequency 3−12 years earlier compared with no drinking

The abstinent group (n=159 women and n=79 men) was used as the reference in regression analysis. The pink and blue bars represent the results for females and males, respectively. The 95% CIs are shown. (Augestad et al. 2008).

A small study with poor internal validity by Otten et al. (2018) enrolled 306 mothers with a mean age of 44 years and 288 fathers with a mean age of 46 years (Table 22). The mean number of drinks consumed by these men and women was used as a continuous variable in regression analysis to correlate drinking quantity at baseline with depressive symptoms measured 4 years later. The authors did not find a significant association between drinking quantity and the emergence of depressive symptoms for either men or women (GRADE ⊕⊖⊖⊖).

Table 22 The correlation between developing depression within 4 years and the mean number of drinks consumed

	N	Follow-up	Correlation coefficient
Women	306	4 years	β=0.05, p=0.36
Men	288	4 years	β=0.01, p=0.87

Source: Otten et al. (2018)

3.1.5 Older adults

Summary:

Both genders combined:

Two studies reported on the risk of drinkers developing depression compared with non-drinkers, with only one study reporting a significant difference. The evidence was therefore inconclusive.

One study compared heavy or at-risk drinkers with non-heavy drinkers and abstainers and found no difference in their risk of developing depression.

One study reported that those who drank at least monthly had reduced odds of having depression at

follow-up compared to those who never drank. No significant difference was found between those who drank daily and those who drank less than daily.

One study assessed the relationship between alcohol and different depressive trajectories (consistently low, consistently high, increasing, or decreasing). Those who abstained or were high-level drinkers were more likely to be in the consistently high depressive symptom group.

Three studies compared the likelihood of developing depressive symptoms among older adults who drank different quantities of alcohol. Two studies compared heavy drinkers with abstainers but only one found a significant increase in the likelihood of developing depressive symptoms. One study compared abstainers, former drinkers and those who drank >1−2 drinks or >2 drinks per day with those who drank >0−1 drink per day. Abstainers and former drinkers were significantly more likely to develop depressive symptoms that those who drank >0−15g per day, and those who drank >15-30 g per day were significantly less likely to develop depressive symptoms. There was no difference in the risk of depression between those who drank >0−15 g per day and those who drank >30 g drink per day.

In females:

Five studies reported on the association between number of drinks consumed per day, and the risk of developing depression compared with abstainers. Four studies were consistent that older women who drank a light to moderate amounts of alcohol had no difference in the likelihood of developing depression compared to those who did not drink. A single large Australian study reported that those who had complete abstinence had significantly higher levels of depression at follow-up than those who consumed 0-20 g/day.

Few elderly people consumed hazardous levels of alcohol, so out of three studies which compared the risk of high levels of alcohol (>20 or 40 g /day) to abstinence, only one study was sufficiently powered, and reported a significant association between heavy drinkers and depression. One study reported that HED had a higher risk of depression compared with abstinence and one study reported no significant difference between HED and non-HED.

When frequent drinking was compared against infrequent drinking, there were no significant differences in the chance of having depression at follow-up.

None of the three studies that reported on the outcome of depressive symptoms reported significant differences based on alcohol exposure measures (frequent drinking, drinking more than once per month, or drinking more than 14 g per day).

In males:

Five studies reported on the association between number of drinks consumed per day, and the risk of developing depression compared with abstainers. Four out of five reported that there was no significant difference in levels of depression between older men who drank light-moderate amounts compared to those who were abstinent. The remaining study reported that those who were abstinent had higher levels of depression than those who drank.

One study reported that short-term-risk drinkers (i.e. who drank >40 g/day) had a higher likelihood of depression than low-risk drinkers. However, two other studies found no significant risk of depression in men drinking above 28 g alcohol per day compared to those who drank less but were not abstinent.

One study reported that there was no difference in the risk of depression between HED and non-HED.

When frequent drinking was compared against infrequent drinking, monthly drinkers were significantly less likely to have depression at follow-up than abstainers.

Sixteen longitudinal cohort studies reported on the likelihood of developing either depressive symptoms or having a depressive episode as a consequence of alcohol intake in older adults. Most studies enrolled adults aged ≥50 years, but two studies enrolled adults aged ≥45 years, and one aged 40−69 years. Ten studies provided data for females and nine studies for males. The risk of bias for the studies reporting outcomes for the total population, and for males and females separately, are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 18. The majority of the studies had a low or moderate risk of bias for internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study, but almost half the studies had a high risk of bias for generalisability to the broader population from which the study participants were selected.

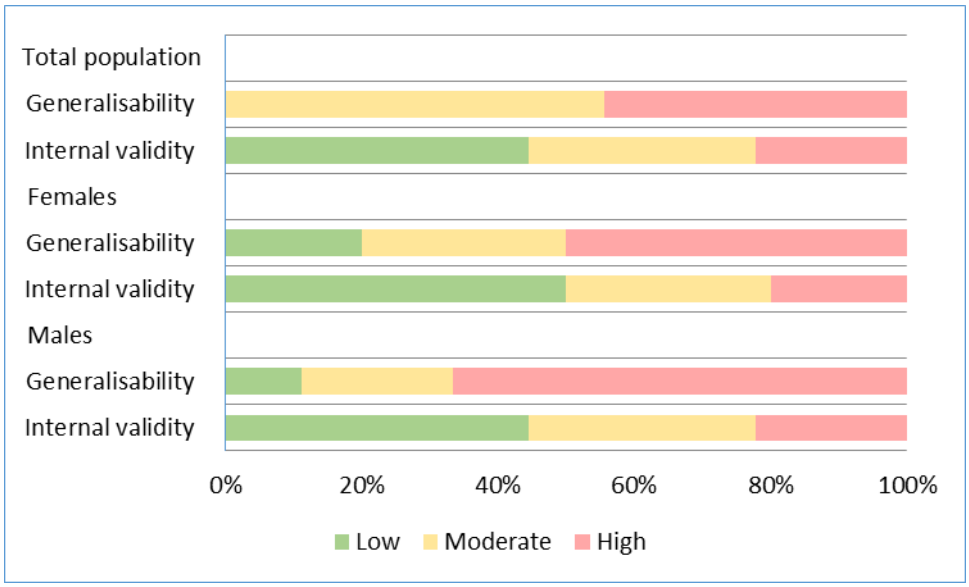


Figure 18 Risk of bias summary for studies reporting depression outcomes for older adults who drank alcohol
Nine studies included results for the total population, ten studies included results for females and nine studies included results for males.

3.1.5.1 Combined gender

Four studies reported the likelihood of older adults developing depression (An & Xiang 2015; Gea et al. 2013; Weyerer et al. 2013) or depressive symptoms (Luppa et al. 2012) due to their alcohol drinking habits compared to abstainers such that the results reflected drinking categories with varying number of drinks/day (Figure 19). The alcohol categories were converted to grams of alcohol/day, and then graphed to show the overlapping groups so that the results could be compared. The German study by Weyerer et al. (2013), had good internal validity and enrolled primary care patients without dementia, aged ≥75 years, and used categories where the number of drinks were equivalent to the same number of Australian standard drinks. The Spanish study by Gea et al. (2013) with moderate internal validity, and the German study by Luppa et al. (2012) with good internal validity, categorised participants, aged ≥55 years and ≥75 years, respectively, according to the grams of alcohol consumed/day and this was converted to Australian standard drinks for the graph below. Tsai et al. (2013) and An & Xiang (2015) categorised participants, aged ≥60 years and ≥50 years, respectively, based on the number of drinks consumed per day.

Only two statistically significant results were reported for these for studies. Gea et al. (2013) found that older adult participants who drank 5−15 g alcohol/day were 30% less likely to develop depression than those who did not drink (GRADE ⨁⊖⊖⊖). Luppa et al. (2012) found that older women who drank ≥20 g alcohol/day and older men who drank ≥30 g alcohol/day were more than

twice as likely to develop depressive symptoms compared with those who drank less (GRADE ⊕⊖⊖⊖).

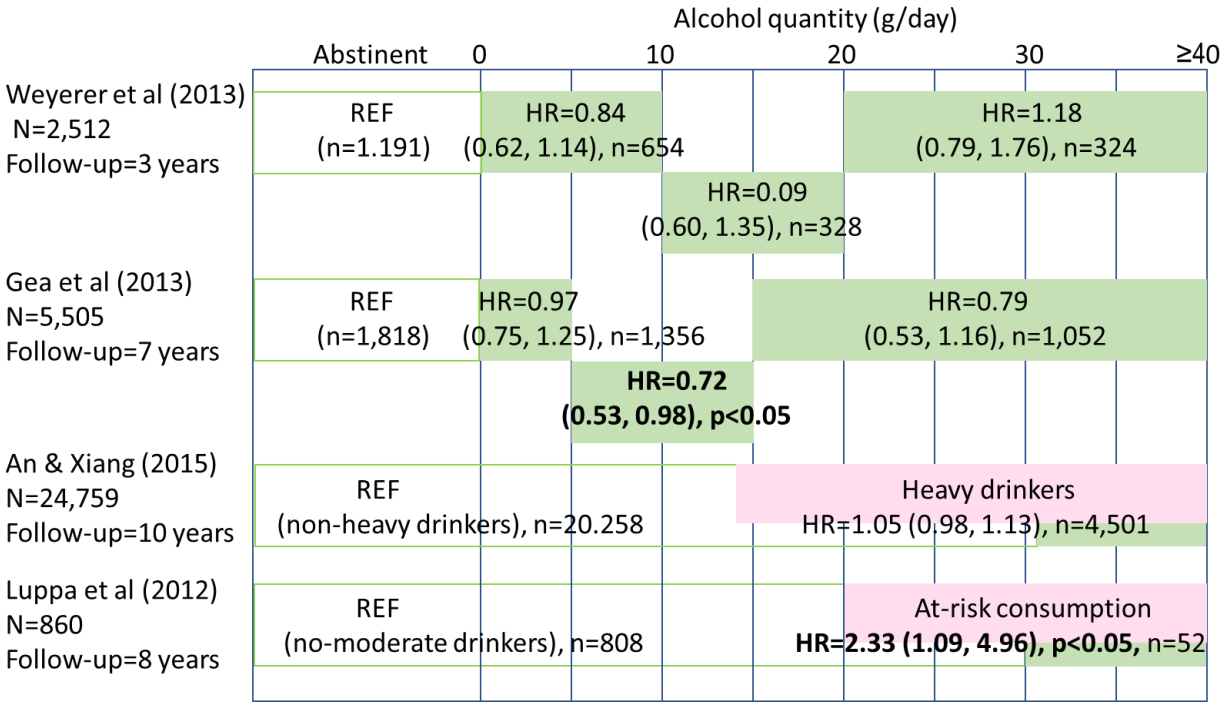


Figure 19 Graph depicting the HR or OR and the 95% CIs for the likelihood of having depressed symptoms among older adults according to their drinking quantity 3−10 years earlier compared with drinking no or little alcohol

The green bars represent the alcohol consumption categories in g/day. The pink bars represent the alcohol consumption for females when it differs from that for males. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. An & Xiang (2015): HRs adjusted for gender, race/ethnicity, education, birth cohort, history of psychiatric problem, smoking, age, marital status, wealth, diagnosis of chronic condition, body weight status. Gea et al. (2013): HRs adjusted for age, gender (for total population only), smoking, physical activity (MET-min/d), total energy intake (Kcal/day), baseline BMI (kg/m2), marital status, intervention group, recruiting centre, educational level and the number of persons living at home. Luppa et al. (2012): HRs were fully adjusted for all variables. Weyerer et al. (2013): HRs fully adjusted for age, gender, living alone, marital status, level of education, mobility impairment, vision impairment, hearing impairment, functional impairment, somatic co-morbidity, mild cognitive impairment, subjective memory impairment, baseline smoking and apoE4.

The American study by Brennan et al. (2016) had poor internal validity with a high risk of bias and investigated the likelihood of adults aged 55−65 years belonging to one of four depressive symptom classes: consistently low, consistently elevated, increasing symptoms and decreasing symptoms in participants according to their specific drinking patterns (**Error! Reference source not found.**). The authors found that over the 10-year follow-up period, participants who drank 0−2 drinks (0−28 g alcohol)/day were almost 2-times more likely to belong to the consistently low class compared to the increasing symptoms class. Conversely, former drinkers were 2.5-times more likely to belong to the increasing symptoms class than the consistently low class. However, former drinkers were also 2-times more likely to belong to the decreasing symptoms class than the consistently low class (GRADE ⊕⊖⊖⊖).

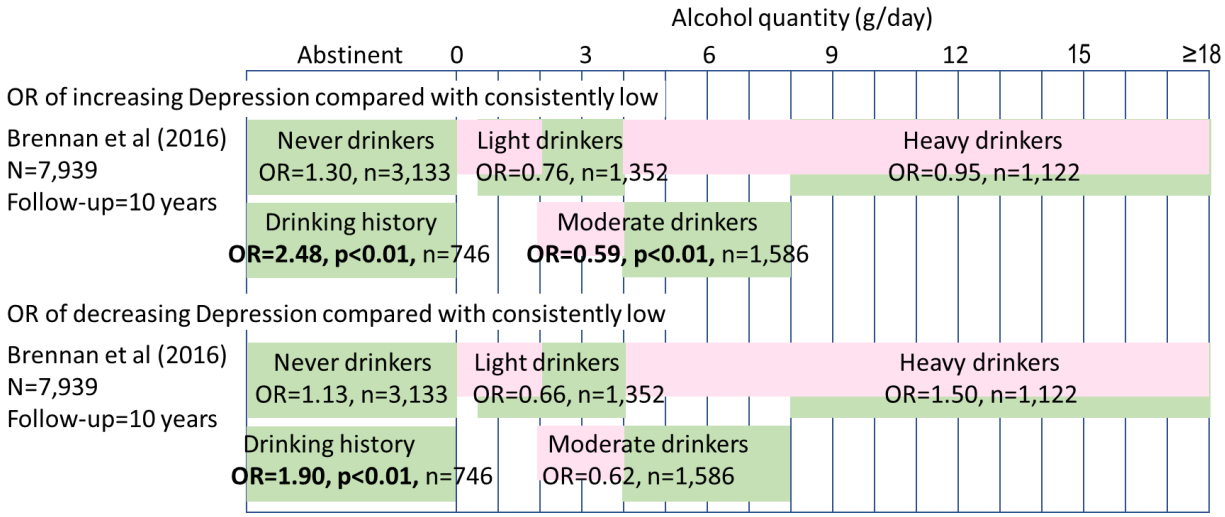


Figure 20 Graph depicting the OR for the likelihood of elderly adults belonging to the increasing depressed symptoms or decreasing symptoms class compared to the consistently low depressive symptoms class according to their drinking habits

The pink and blue bars represent the number of drinks/day included in each drinking category for females and males, respectively. The p=values are shown for statistically significant results, which are also in boldface. ORs were adjusted for the number of medical conditions at baseline. (Brennan et al. 2016)

Two studies reported on the effect of drinking frequency on the likelihood of developing depressive symptoms 2−8 years later (Table 23). The Chinese study with poor internal validity by Cheng et al. (2016) categorised the participants, aged ≥45 years, according to how frequently they drank alcohol and found that those who drank at least monthly were 40% less likely to develop depressive symptoms than those who never drank (GRADE ⊕⊖⊖⊖). When those who never drank were used as the reference group, the unadjusted OR (95% CI) from bivariate linear regression analysis indicated that those who drank at least monthly were 40% less likely to have depression (GRADE ⊕⊖⊖⊖).

The Taiwanese study by Tsai et al. (2013) had good internal validity and included adults aged 60 years and over. Participants were grouped according to their drinking frequency (less than or more than weekly) and weekly drinkers were further subdivided into moderate drinkers (less than 2 drinks per occasion) and heavy drinkers (more than 2 drinks per occasion). However, the amount of alcohol consumed is uncertain as Taiwan has not reported a standard alcoholic drink measure. However, although the point estimate for heavy weekly drinkers suggested a 30% reduction in the likelihood of developing depressive symptoms compared with less than weekly drinkers, this was not statistically significant (GRADE ⊕⊕⊕⊖).

Table 23 The OR (95% CI) for developing depressive symptoms within 2 years and drinking frequency

<table>
<tr><th>Never drinker</th><th>Former drinkers</th><th>Monthly drinker</th><th>Weekly drinker</th><th>Daily drinker</th></tr>
<tr><td colspan="5">Cheng et al. (2016), N=17,708</td></tr>
<tr><td>REF</td><td>OR=0.8 (0.5, 1.1)</td><td colspan="3">OR=0.6 (0.5, 0.7), p<0.05, n=4,383</td></tr>
<tr><td colspan="4">REF: less than daily</td><td>OR=1.2 (0.8, 1.7), n=783</td></tr>
<tr><td colspan="5">Tsai et al. (2013), N=3,273</td></tr>
<tr><td colspan="3" rowspan="2">REF: less than weekly drinkers, n=2,629</td><td colspan="2"><u>Moderate at least weekly drinker (<2 drinks/time)</u>
OR=0.89 (0.63, 1.26), n=570</td></tr>
<tr><td colspan="2"><u>Heavy at least weekly drinker (≥2 drinks/time)</u>
OR=0.70 (0.30, 1.64), n=74</td></tr>
</table>

The green shading represents statistically significant results. Cheng et al. (2016): OR are unadjusted. Tsai et al. (2013): ORs adjusted for gender, age, level of education, psychological stress, diabetes, heart disease, Instrumental Activities of Daily Living status, family support, and audio acuity.

Two studies with moderate internal validity reported on the association of depressive symptoms with earlier drinking quantities (Figure 21). The English study by Lang et al. (2007) included adults aged ≥50 years and reported that fewer depressive symptoms were associated with moderate levels of alcohol consumption than with never having drunk any alcohol. The American study by Paulson et al. (2018) found that moderate alcohol use predicted fewer depressive symptoms among older adults, aged >65 years, compared with abstinence (GRADE ⨁⨁⊖⊖).

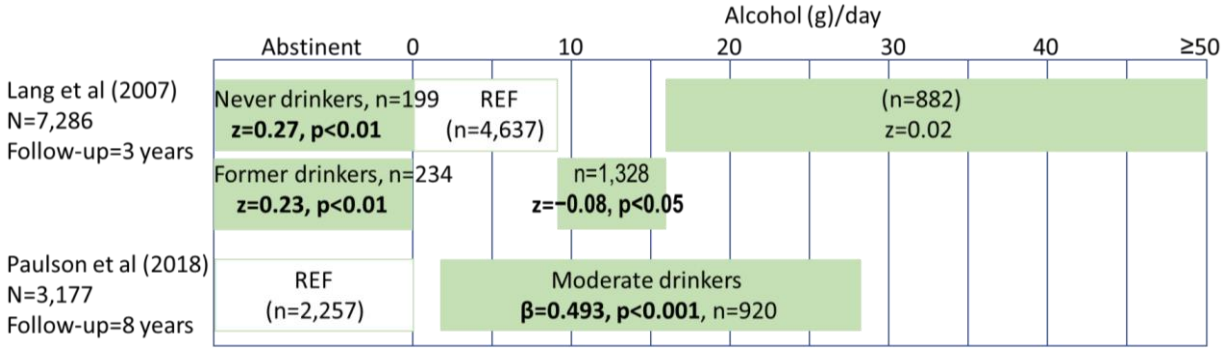


Figure 21 The association between developing depressive symptoms within 3−8 years and the number of drinks consumed

The green bars represent the alcohol consumption categories in g/day. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. Lang et al. (2007): Linear regression z-scores (95% CI), analyses controlled for: age; gender; BMI; education level; smoking; co-morbidity; income; household wealth; participation in moderate or vigorous exercise; number of close family members; number of close friends. Paulson et al. (2018): Slope-intercept model predicting depressive symptomatology. Baseline differences in depressive symptoms between moderate drinkers and abstainers narrowed over time (benefits of moderate drinking eroded by passage of time).

3.1.5.2 Female and male subgroup analysis

Three studies reported the OR or HR (95% CI) for the likelihood of developing depression according to number of drinks consumed per day in older men and women separately, or in women alone, using abstinence as the reference group (Figure 22). The alcohol categories were converted to grams of alcohol/day, and then graphed to show the overlapping groups so that the results could be compared.

A Spanish study by Gea et al. (2013), with moderate internal validity, included adults aged ≥55 years and compared the incident rate of depression among those who drank <5 g, 5−15 g/day or >15 g of alcohol/day with that among abstainers over a 7-year period. An Australian study with good internal validity by Hiles et al. (2015) included older adults aged 55−85 years and compared the likelihood of developing depressive symptoms over 3.5−5.5 years in the three alcohol consumption groups compared to non-drinkers. The Japanese study by Tanaka et al. (2011) had moderate internal validity and enrolled middle-aged and older adults aged 40−69 years and investigated the likelihood of light or heavy drinkers developing depression over 7 years compared with non-drinkers. One Japanese standard drink contains 19.75 g of alcohol, so light drinkers in Japan are likely to consume more alcohol than Australian light drinkers. The study did not define how many drinks light and heavy drinkers consumed, but using the current Australian guidelines as no more than 2 drinks/day for healthy use, we can assume that Japanese light drinkers would consume up to 40 g alcohol/day and heavy drinkers would consume more. The American study with good internal validity by Chang et al. (2016) enrolled older women aged ≥65 years and investigated the likelihood of developing depression over 10 years in moderate and HED/heavy drinkers compared to those who did not drink.

Only the study by Chang et al. (2016) reported a statistically significant outcome (Figure 22). The authors found that older women who drank more than 3 drinks (42 g alcohol)/day were 13% more likely to develop depression over the following 10 years compared to women who did not drink. The older women who drank between 0 and 2 drinks (0−28 g alcohol)/day were 7% less likely to develop depression than those who did not drink but this outcome did not quite reach statistical significance as the upper 95% CI was 1.0 (GRADE ⨁⊖⊖⊖). Likewise Gea et al. (2013) found that older men who drank 5−15 g alcohol/day were half as likely as those who did not drink to develop depression, but the upper 95% CI was also 1.0 for this outcome.

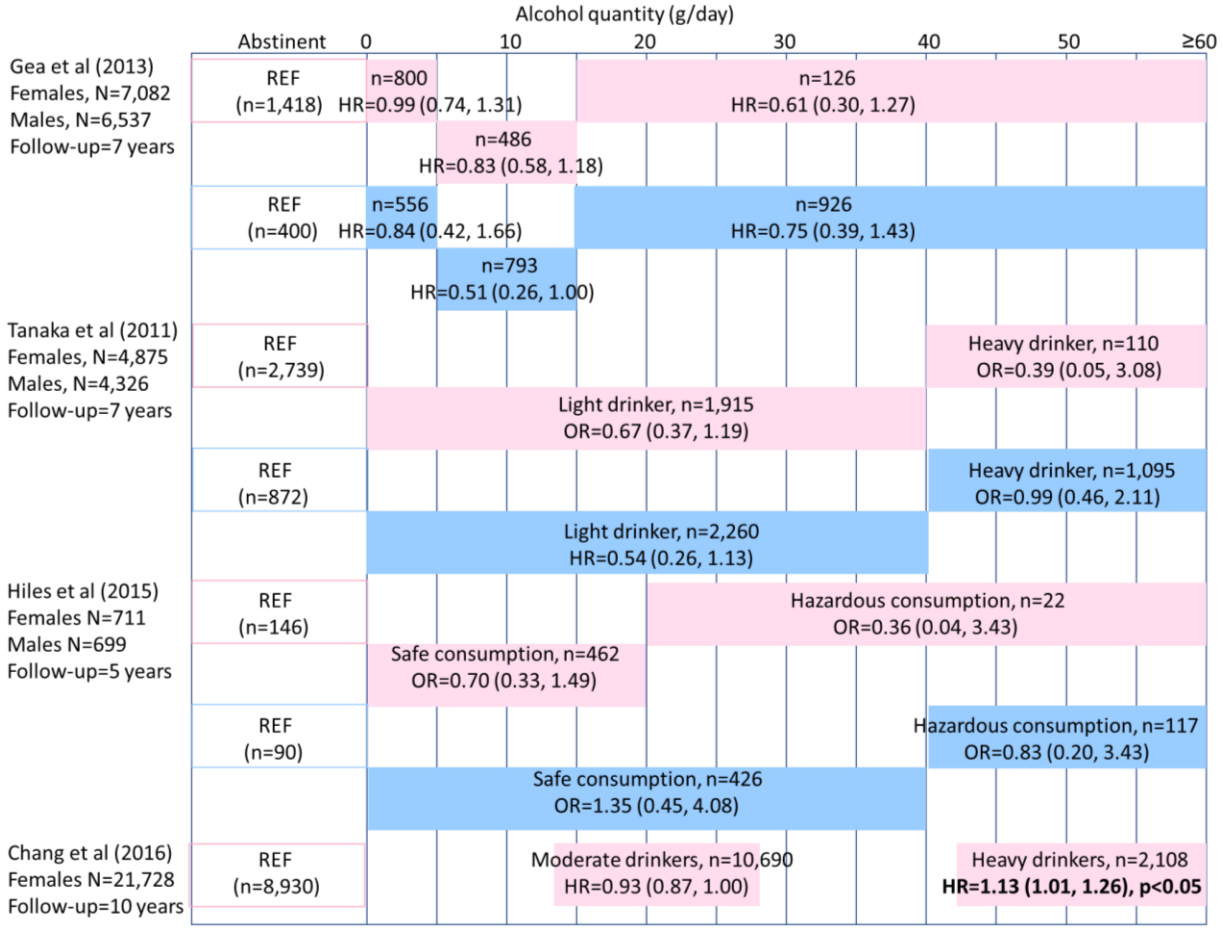


Figure 22 Graph depicting the HR, OR and the 95% CIs for the likelihood of having depressed symptoms within 5−10 years among older women and men according to their drinking quantity compared with drinking no alcohol

The pink and blue bars represent the number of drinks/day included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each category are also shown. Chang et al. (2016): HRs adjusted for age, and time-varying covariates (education, race, social network, body mass index, diet, cigarette smoking, vigorous activity, co-morbidities, and hours of sleep per day). Gea et al. (2013): RRs adjusted for age, smoking, physical activity, total energy intake, baseline BMI, marital status, intervention group, recruiting centre, educational level and the number of persons living at home. Hiles et al. (2015): ORs adjusted for age, CES-D score, IL-6 level, CRP, waist-to-hip ratio, BMI, Steps per day, % energy intake from saturated fat, physical health problems, Quality of Life score; independent living, relationships, coping and pain. Tanaka et al. (2011): ORs adjusted for age, area, education, occupation, social network (marriage, household, neighbourhood, participation, and friends.

Three studies reported OR or HR (95% CI) for the likelihood of developing depression or depressive symptoms according to number of drinks consumed per day in older men and/or women separately using both abstinent and low level drinkers in the reference group (Figure 23).

The American study with moderate internal validity by An & Xiang (2015) enrolled adults aged ≥50 years and compared the likelihood of developing depression over 10 years in heavy drinkers compared to non-heavy drinkers. Heavy drinking was defined as ≥1 drink (women: 14 g alcohol) or ≥2 drinks (men: 28 g alcohol) per day or ≥4 drinks on any occasion in past 3 months. The study by Bots et al. (2008) was conducted in Finland, Italy and the Netherlands, and had good internal validity. Older males with mean age 75 years were enrolled and the odds of those with moderate (1-31 g) or high (>31 g) daily alcohol consumption developing depressive symptoms over 5 years were compared to those who drank an average of less than 1 g of alcohol /day. Byers et al. (2012) included older females aged ≥65 years and compared the odds of those drinking frequently developing depressive symptoms over a mean 12-year follow-up period compared to infrequent drinkers. Frequent drinkers were defined as having ≥7 drinks/week, which is equivalent to ≥1 drink (≥14g alcohol)/day. It was concluded that in women, there was evidence of no association between either heavy drinking or having more than one drink per day and subsequent depression (GRADE ⊕⊕⊖⊖ to ⊕⊕⊕⊖).

Only the study by Bots et al. (2008) reported a statistically significant outcome (Figure 23). They found that older men who drank ≥1 drink/week and up to 3 drinks/day had a greatly reduced likelihood of developing depression over the next 5 years compared to those who drank less than once/week.

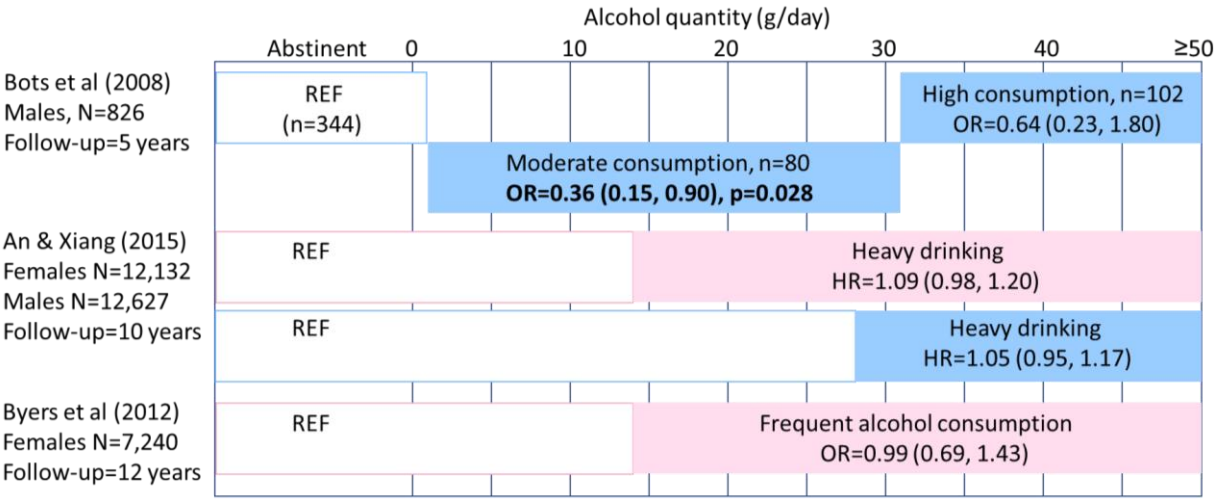


Figure 23 Graph depicting the HR, OR and the 95% CIs for the likelihood of having depressed symptoms within 3–12 years among older women and men according to their drinking quantity compared with drinking less than the drinking categories of interest

The pink and blue bars represent the number of drinks/day included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each category are also shown when reported by the study. An & Xiang (2015): HRs adjusted for gender, race/ethnicity, education, birth cohort, history of psychiatric problem, smoking, age, marital status, wealth, diagnosis of chronic condition, body weight status. Bots et al. (2008): ORs adjusted for baseline depressive symptoms, physical activity, and change in cholesterol. Byers et al. (2012): ORs adjusted for education, married, living alone.

One Australian study with poor internal validity by Tait et al. (2012) investigated the likelihood of abstainers and high-risk drinkers developing depression compared to those who drank ≤2 standard drinks/day and were at low risk of developing health problems. High-risk drinkers were divided into those with an increased risk of long-term harms (e.g. cancer; >2–≤4 standard drinks/day) and those with an increased risk of short-term harms (e.g. accidents, >4 standard drinks/day). The results have been graphed after converting Australian standard drinks into grams of alcohol/day (Figure 24). This study included adults aged ≥45 years and found that older women who did not drink and those who drank more than 20g alcohol/day were at greater risk of developing depression within 4 years than those who drank less than 20 g alcohol/day (GRADE ⊕⊕⊕⊖). Similarly older men who did not

drink and those who drank more than 40 g alcohol/day were at greater risk of developing depression within 4 years than those who drank less than 20 g alcohol/day (GRADE ⊕⊕⊕⊖).

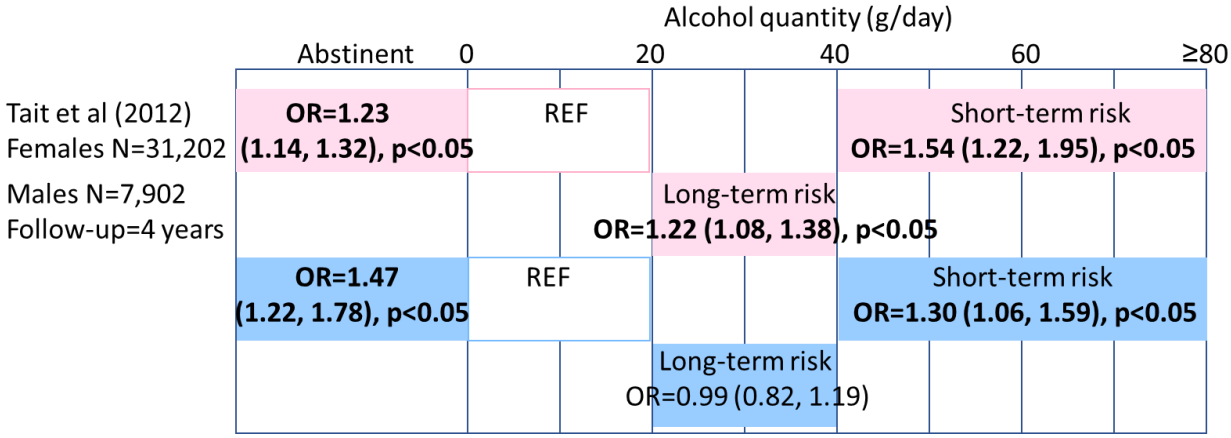


Figure 24 Graph depicting the OR (95% CI) for the likelihood of having depression within 4 years among older women and men according to their drinking quantity compared with drinking 0–2 drinks/day

The pink and blue bars represent the number of drinks/day included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. Tait et al (2012) used GEE models implemented in SPSS version 19 and specified an unstructured working correlation matrix.

The American study with good internal validity by Chou, Liang & Mackenzie (2011) included middle aged and older adults aged ≥50 years, and compared the likelihood developing MDD over 3 years according to HED frequency compared to non-drinkers. The authors found only one significant result. Older men who were abstinent were 60% more likely to develop depression than non-HED participants (Figure 25). There was no significant association in older women (GRADE ⊕⊕⊕⊖).

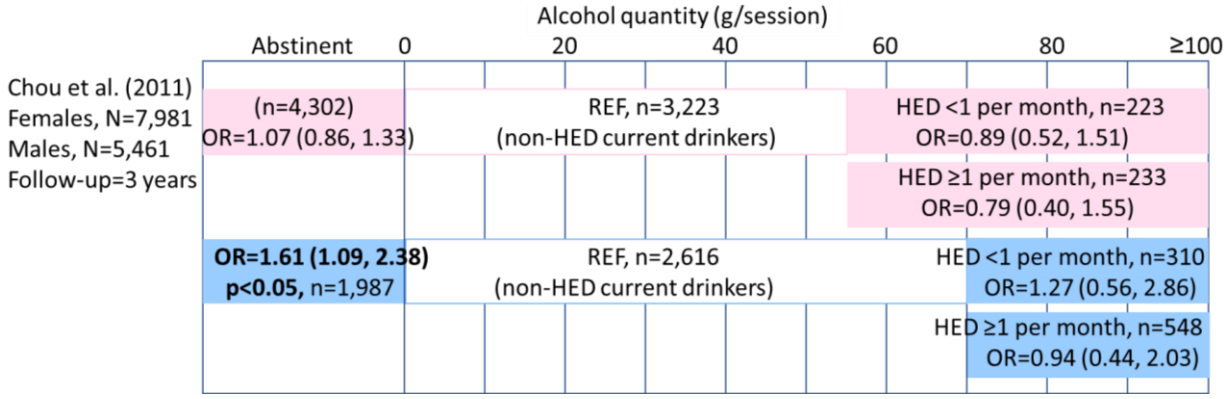


Figure 25 Graph depicting the OR (95% CI) for the likelihood of having MDD within 3 years among older women and men according to HED frequency

The pink and blue bars represent the number of drinks/session included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets, the number of participants per category are also indicated and statistically significant results are shown in boldface.

The study by Cheng et al. (2016) was conducted in China and had poor internal validity. The adult participants aged ≥45 years were categorised as never drinkers, former drinkers and current drinkers. Current drinkers were defined as having drunk alcohol more than monthly in the last year. They used the never drinkers and former drinkers as the reference groups in separate analyses (Table 24). The authors reported that older men who drank more than once per month were 30% less likely to develop depressive symptoms than those who were abstinent (GRADE ⊕⊖⊖⊖).

Table 24 The OR (95% CI) for the likelihood of developing depressive symptoms within 2 years in older men and women drinking more than once a month

	Never drinker	Former drinkers	Monthly drinker	Weekly drinker	Daily drinker
Women	REF		OR=0.8 (0.5, 1.3)		
N=8,175		REF	OR=1.3 (0.5, 3.8)		
Men	REF		OR=0.7 (0.5, 0.9), p<0.05		
N=2,683		REF	OR=0.8 (0.6, 1.3)		

Blue cell represents a statistically significant result. Cheng et al. (2016): ORs were adjusted for age, baseline tobacco use or drinking status, baseline health status and changes in marital status.

The English study by Lang et al. (2007) had moderate internal validity and included adults aged ≥50 years and classified them as ex-drinkers, never-drinkers, >0−1 drink (14 g of alcohol)/day, >1−2 drinks (15−28 g of alcohol)/day, >2 drinks (>28 g of alcohol)/day. The authors used those drinking up to 1 drink/day as the reference group and reported the linear regression z-scores for the association between developing depressive symptoms within 3 years and the number of drinks consumed in older men and women (Figure 26). They reported that fewer depressive symptoms were associated with moderate levels of alcohol consumption than with never having drunk any in both older men and women (GRADE ⨁⨁⊖⊖).

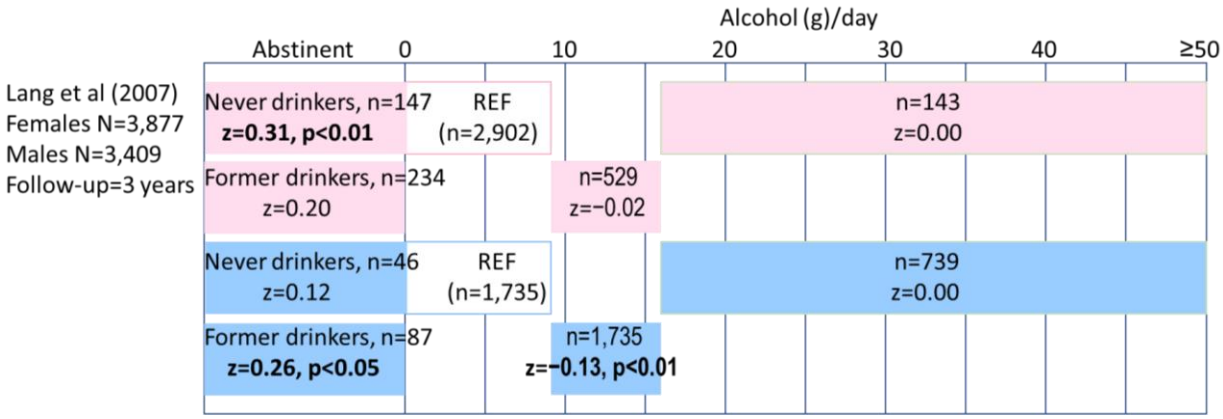


Figure 26 Linear regression z-scores for the association between developing depressive symptoms within 3 years and the number of drinks consumed in older men and women

The pink and blue bars represent alcohol consumption in g/day for each drinking category for females and males, respectively. The number of participants per category are indicated and the statistically significant results are shown in boldface. OR adjusted for age, marital status, education, race, household income, employment status, lifetime history of DSM-IV mood and anxiety disorders at Wave 1 assessment, and lifetime history of alcohol use disorder at Wave 1 assessment.

3.2 The effect of alcohol consumption on developing bipolar disorder

Summary:

Two publications from a single large study assessed the association between alcohol consumption and the development of bipolar disorder in the general population (rather than targeting a subgroup exposed to trauma).

One publication reported that adults of any age who drank less than weekly (or abstained), had higher levels of incident bipolar disease than those who drank alcohol on a weekly basis. The second publication found that there was no difference in the likelihood of incident bipolar disorder in men or women who were abstinent or participated in HED compared to those who drank without participating in HED.

The NESARC is a large national study performed in the United States. Two publications from this study reported on the association between alcohol consumption (HED or weekly consumption) and first-episode bipolar disorder. As both articles poorly described the source population, there is a high risk of bias for the generalisability of these results (see Appendix D in the Technical Report).

3.2.1 All ages

One study with good internal validity by Cougle et al. (2015) had moderate internal validity and included data from adults of any age. The authors reported that weekly alcohol use at wave 1 was related to a reduced risk of developing bipolar disorder at wave 2 (Table 25). There is therefore *limited evidence of an association* between alcohol consumption and risk of developing bipolar disorder (GRADE ⊕⊕⊖⊖).

Table 25 The association between alcohol consumption and incident bipolar disorder

Population	Results
N=34,653 adults (nationally representative survey of non-institutionalised US citizens)	**OR (95%CI) for incident bipolar disorder at wave 2** Reference: not stated (assume consumption of alcohol less than weekly) Weekly alcohol: OR_{adj}= 0.79 (0.73, 0.86), p<0.001

Cougle et al. (2015): OR adjusted for age, income, marital status, gender, ethnicity, education, and psychiatric comorbidity.

3.2.2 Older adults

A study by Chou, Liang & Mackenzie (2011), with good internal validity reported on the relationship between HED and incident bipolar disorder in the middle-aged and older adult subgroup of the NESARC study and found no significant relationship in males or females (Figure 27). There is *no evidence of an association* between HED frequency and bipolar disorder in either males or females (GRADE ⊕⊕⊕⊖).

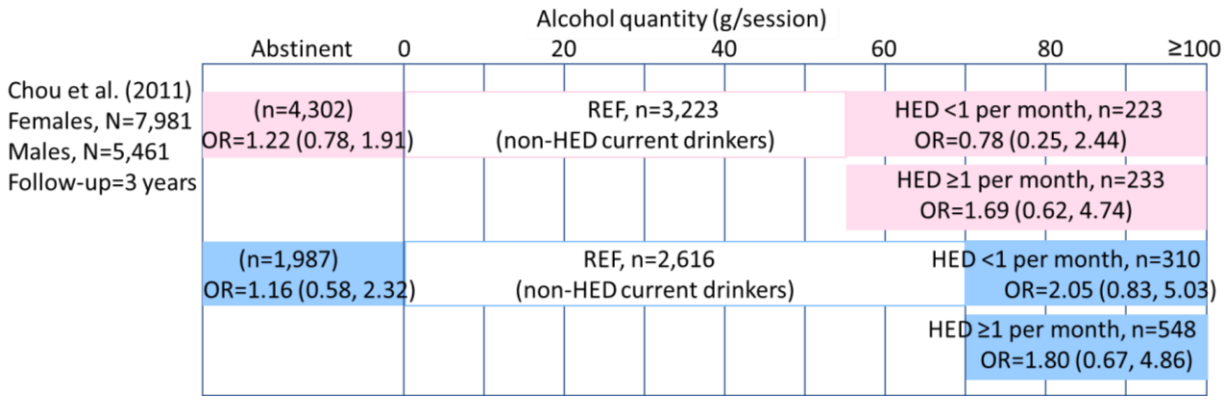


Figure 27 Graph depicting the OR (95% CI) for the likelihood of having bipolar disorder within 3 years among older women and men according to HED frequency

The pink and blue bars represent the number of drinks/session included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of males and females in each category was not reported.

3.3 The effect of alcohol consumption on suicidal ideation, attempts and completed suicides (general population)

Nine cohort studies reported on the likelihood of suicidal ideation or attempting suicide as a consequence of alcohol intake. Two studies reported longitudinal findings and seven were a cross-sectional design that cannot distinguish between cause and effect. Five of the studies included an adolescent population.

The risk of bias for all of the studies and those reporting outcomes for adolescents, are presented for individual studies in Appendix D in the Technical Report and are summarised inFigure 1. The majority of the studies had a low or moderate risk of bias for both the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and its generalisability to the broader population from which the study participants were selected.

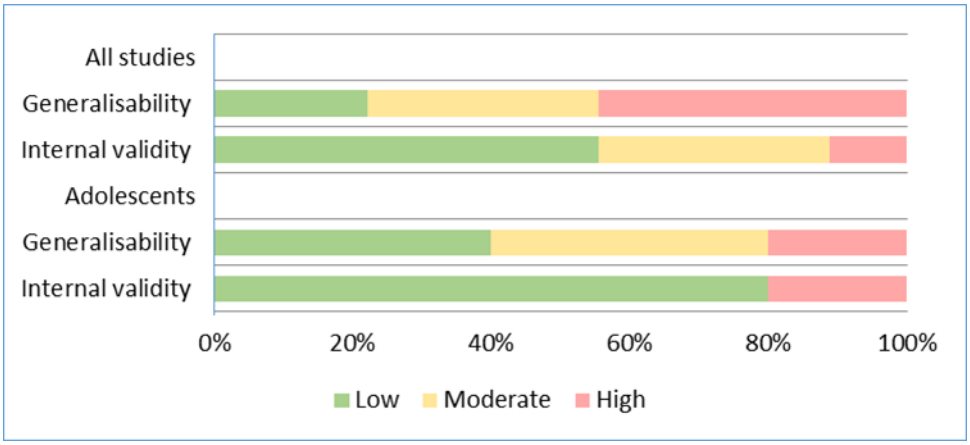


Figure 28 Risk of bias summary for studies reporting suicide outcomes for individuals who drank alcohol
Nine studies included results for any population and five studies included results for adolescents.

3.3.1 All ages

Summary:

In adjusted analyses, having a MDE interacted with HED. In both males and females without MDE, those who had participated in HED in the past month were 50% more likely to have suicidal ideation or attempt suicide than their non-HED counterpart. However, there was no difference in those with MDE.

A single cross-sectional study with moderate internal validity was identified in a large sample of men and women (≥18 years) from the United States (n=136,500), on the association between frequency of HED (drinking over 5 standard drinks or 70 g alcohol within a couple of hours) in the previous month, and suicidal ideation or suicide attempts over the previous 12 months (Glasheen et al. 2015). In unadjusted analyses, HED was a significant predictor of both suicidal ideation and suicide attempts in both males and females (Figure 29). In adjusted analyses, having a MDE interacted with HED. In both males and females *without* MDE, those who had participated in HED in the past month were 50% more likely to have suicidal ideation than their non-HED counterparts. However, in those *with* MDE, those who participated in HED *did not* have an increased risk of suicidal ideation compared to those who did not participate in HED. Therefore, there is *limited evidence of an association* between HED and suicidal ideation and suicide attempts in both men and women (GRADE ⨁⊖⊖⊖).

For suicide attempts, the results were similar. In females without MDE, those who had participated in HED in the past month were 2.6-times more likely to attempt suicide than their non-HED counterparts, but although the point estimate for males showed a 50% increased likelihood, it did not reach statistical significance. In both males and females with MDE, those who participated in HED *did not* have an increased risk of attempted suicide compared to those who did not participate in HED. Therefore, there is *limited evidence of an association* between HED and suicide attempts in women and there is *no reliable evidence of an association* in men (GRADE ⨁⊖⊖⊖).

In females, the Wald test for interaction between HED and MDE on suicide attempts, indicated that the association between HED and suicide attempts was not equal in females with and without MDE (adjusted Wald χ^2=14.58(1), p<0.001). However, the interaction was not significant among males (adjusted Wald χ^2=0.01(1), p=0.989) There is *limited evidence of an association* between MDE, HED and suicide attempts in women and there is *no reliable evidence of an association* in men (GRADE ⨁⊖⊖⊖).

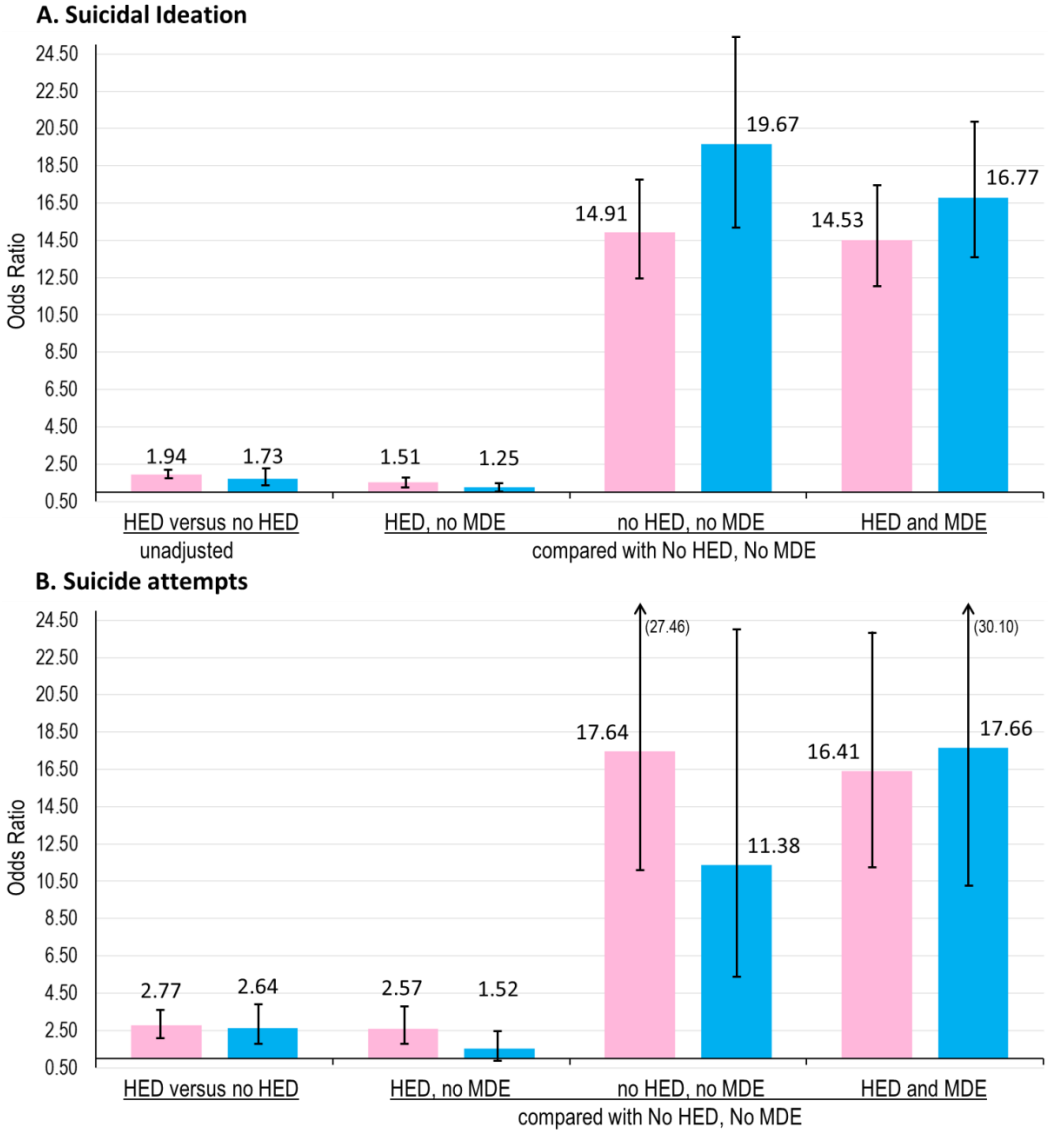


Figure 29 Bar graph depicting the OR (95% CI) for the likelihood of having suicidal thoughts (A) and attempting suicide (B) if participating in HED compared with no HED, and its interaction with MDE

The pink and blue bars represent the results for females and males, respectively. The 95% CIs are shown. ORs for interaction of HED with MDE were adjusted for age, race/ethnicity, marital status, education, employment, income, illicit drug abuse/dependence. (Glasheen et al. (2015).

3.3.2 Adolescents

Summary:

Two large cross-sectional studies reported that both HED and drunkenness in the past month were significantly associated with suicidal ideation and/or suicide attempts in adolescents. In further analyses, one of these studies determined that the association between 'drinking while down' and suicide attempt was much stronger than for HED, and so the motive for drinking was more important than the occurrence of HED.

A second cross-sectional study reported that adolescents who drank alcohol in the past month were more likely to also have suicidal ideation than those who were abstinent. Another large cross-sectional study reported that those who had started drinking alcohol as a pre-teen or teen were more likely to have suicidal ideation and more likely to attempt suicide than those who did not consume alcohol. However, the direction of effect cannot be determined in these studies.

Two cross-sectional studies reported consistent evidence that girls and boys who start consuming alcohol before age 12 or 13 have a higher risk of having suicidal thoughts than those who do not start drinking alcohol. Those who started drinking as a teen also had a higher risk than those who did not.

Two cross-sectional studies reported consistent evidence that girls who start consuming alcohol before age 12 or 13 have a higher risk of attempting suicide than those who do not start drinking alcohol. Those who started drinking as a teen also had a higher risk than those who did not. When the sexes were assessed separately, the two studies both reported that that boys who start consuming alcohol as a teen are not at an increased risk of suicide attempt compared to those who have not started drinking.

3.3.2.1 Combined gender

Four cross-sectional studies were identified which reported on the association between alcohol consumption and suicidal ideation or attempts in adolescents. Two large studies focused on the association between HED and suicidal ideation or suicide attempts (Gart & Kelly 2015; Schilling et al. 2009), one study assessed the association between age of initiation of drinking on suicidal ideation or attempts (Peltzer & Pengpid 2015), and one study looked at the association of any past-month alcohol consumption or drunkenness on suicidal ideation (Souza et al. 2010).

The two large studies reporting on the association between HED (≥70g of ethanol within a couple hours) and suicidal ideation and suicide attempts were both from the United States. Gart & Kelly (2015) had poor internal validity and reported that HED was associated with a small but significant increase in the likelihood of suicidal ideation, and an even larger likelihood of suicide attempt (Their results were consistent, that those who started consuming alcohol (volume and frequency not specified) prior to turning 12 or 13 years of age, had a significantly greater risk of having suicidal ideation and attempting suicide than non-initiators. The studies were also consistent that females who initiated alcohol consumption after age 12 or 13, also had increased risks, whereas for males, teen alcohol initiation was associated with an increased risk of suicidal ideation, but not a significantly increased risk of suicide attempt.

Therefore, there is *limited evidence of an association* initiation of alcohol consumption as a preteen and suicide attempts for both males and females. There is also *limited evidence of an association* initiation of alcohol consumption as a preteen and suicidal ideation for females, but *no reliable evidence of an association* for males (GRADE ⊕⊕⊖⊖).

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The other study with good internal validity by Schilling et al. (2009) sought to distinguish between suicide attempts which had been planned (prior suicidal ideation), and those which were unplanned, or impulsive. Consistent with Gart & Kelly (2015), they reported that HED was associated with a significant increased likelihood of suicide attempts. The authors also reported that prior suicidal ideation increased the risk of a suicide attempt 38-fold compared to no prior suicidal ideation. However, the coefficient for the interaction between HED and suicidal ideation was not significant on the likelihood of suicide attempt, meaning that the association between HED and suicide attempts did not differ between those who had suicidal ideation or not (Table 26)

Drinking alcohol while down, significantly predicted the likelihood of suicide attempt with a reported 75% increased risk. Furthermore, there was a significant interaction between drinking while down, and suicidal ideation. In those adolescents who did not have suicidal ideation, drinking while down was associated with a threefold increase in suicide attempt compared with a 68% increase in those who did.

There is *limited evidence of an association* between HED and both suicidal ideation and suicide attempts (GRADE ⨁⊖⊖⊖).

Table 26 Association between HED and suicidal ideation or suicide attempt

Study	Predictor	Suicidal ideation	Suicide attempts
Gart & Kelly (2015) N=15,363	HED	n=12,456 *B*=0.02, β=0.02, p=0.027	n=11,159 *B*= 0.03, β=0.05, p<0.001
Schilling et al. (2009) N=31,953	HED (1-year prevalence=29.2%)		*B*=0.20 (0.06, 0.34), p<0.05 HED * Ideation interaction: *B*=−0.40, (−0.80, 0.01)
	Drinking while down (1-year prevalence=12.2%)	All adolescents Prior ideation YES: NO:	*B*=0.56 (0.42, 0.69), p<0.05 OR=1.68 (1.46, 1.93) OR=3.02 (2.03, 4.49) Drinking while down * Ideation interaction: *B*=−0.59, SE=0.21 (−1.01, −0.18), p<0.05
	Suicidal ideation reported in past year		*B*=3.64 (3.39, 3.90), p<0.05 OR=38.2 (29.6, 48.3)
	Depressive symptoms in past year		*B*=0.13 (0.10, 0.15), p<0.05

The green shading represents statistically significant results. Gart & Kelly (2015): Multiple regression analysis of predictors of suicidal ideation and suicide attempt. Schilling et al. (2009): Multivariate logistic regression model predicting suicidal ideation and suicide attempts

One cross-sectional study with good internal validity reported on the association between age of alcohol initiation and the likelihood suicidal ideation or suicide attempt. Peltzer & Pengpid (2015) studied adolescents aged 13−16 years from four different Pacific Island countries. The authors reported that all adolescents who started consuming alcohol (volume and frequency not specified), regardless of age at initiation, had significantly higher risks of having suicidal ideation and attempting suicide compared with non-initiators. However, those who started consuming alcohol prior to turning 12 years of age, had approximately double the risk of having suicidal ideation and attempting suicide than those who stated drinking after turning 12 years of age. There is *limited evidence of an association* between HED and both suicidal ideation and suicide attempts (GRADE ⨁⨁⊖⊖).

Table 27 Adjusted OR (95%CI) of suicidal ideation and suicide attempts by age of initiation of alcohol consumption

Outcome	Non-initiators	Teen initiators	Preteen
Suicidal ideation N=6,540	REF: OR=1.00	**≥12 years** OR=1.95 (1.32, 2.89)	**<12 years** OR=3.39 (2.44, 4.71)
Suicide attempts N=6,540	REF: OR=1.00	**≥12 years** OR=1.64 (1.16, 2.32)	**<12 years** OR=4.55 (3.34, 6.21)

The green shading represents statistically significant results. OR adjusted for age, psychological distress and current alcohol use. (Peltzer & Pengpid 2015)

A single study with good internal validity by Souza et al. (2010) reported on the association between any either alcohol consumption or drunkenness within the past month (quantity or frequency not stated) and suicidal ideation. This study focused on adolescents from an urban area of Brazil, adjusting for the key confounding factors and had a low risk of bias. The authors reported that those who consumed alcohol in the previous month, had a significantly greater chance of having suicidal ideation in the previous 12 months than those who did not consume alcohol (Table 28). There is *limited evidence of an association* between alcohol consumption initiation and both suicidal ideation and suicidal ideation (GRADE ⊕⊕⊖⊖).

There was a similar trend suggesting that those who got drunk were at a higher risk of having suicidal ideation in an unadjusted analysis, however, this was no longer significant after adjusting for covariates. Given the cross-sectional nature of the study, it is unknown whether the associations identified were due to adolescents using alcohol to cope with suicidal ideation, or whether alcohol increased the likelihood of suicidal ideation. There is *no evidence of an association* between alcohol consumption initiation and both suicidal ideation and suicidal ideation (GRADE ⊕⊕⊖⊖)

Table 28 Adjusted OR (95%CI) of suicidal ideation due to alcohol consumption or drunkenness in the past month

Outcome	Reference	Alcohol consumption	OR (95%CI)
Suicidal ideation N=1,039	No alcohol consumption	Drank alcohol in past month	OR=1.64 (1.04, 2.58), p=0.033
	Did not get drunk	Got drunk in past month	OR=1.94 (0.86, 4.36)

The green shading represents statistically significant results. ORs adjusted for gender, age and socioeconomic status, sexual intercourse, alcohol consumption, drunkenness, tobacco use, and use of illicit drugs in previous month, symptoms of conduct disorder and high depressive symptoms. (Souza et al. 2010)

3.3.2.2 Female and male subgroup analysis

Two cross-sectional studies with good internal validity were identified which reported on the association between alcohol consumption and suicidal ideation or suicide attempts in adolescent males and females, separately (Kim & Kim 2010; Peltzer & Pengpid 2015). Both studies assessed the association between age of initiation of drinking on suicidal ideation or attempts.

Their results were consistent, that those who started consuming alcohol (volume and frequency not specified) prior to turning 12 or 13 years of age, had a significantly greater risk of having suicidal ideation and attempting suicide than non-initiators. The studies were also consistent that females who initiated alcohol consumption after age 12 or 13, also had increased risks, whereas for males, teen alcohol initiation was associated with an increased risk of suicidal ideation, but not a significantly increased risk of suicide attempt.

Therefore, there is *limited evidence of an association* initiation of alcohol consumption as a preteen and suicide attempts for both males and females. There is also *limited evidence of an association*

initiation of alcohol consumption as a preteen and suicidal ideation for females, but *no reliable evidence of an association* for males (GRADE ⊕⊕⊖⊖).

Table 29 Odds ratio (95%CI) of suicidal ideation or suicide attempt by age of initiation of alcohol consumption

Study	Non-initiators	Teen initiators	Preteen
Suicidal ideation			
Kim & Kim (2010)			
Females, n=31,467	REF, n=12,251	OR=1.21 (1.12, 1.30), n=14,442	OR=1.45 (1.33, 1.59), n=4,774
Males, n=32,417	REF, n=12,356	OR=1.11 (1.01, 1.22), n=13,595	OR=1.28 (1.16, 1.41), n=6,466
Peltzer & Pengpid (2015)			
Females, n=3534	REF	OR=2.12 (1.34, 3.34)	OR=3.12 (1.95, 4.90)
Males, n=2846	REF	OR=1.88 (1.14, 3.10)	OR=3.37 (2.16, 5.27)
Suicide attempts			
Kim & Kim (2010)			
Females, n=31,467	REF, n=12,251	OR=1.23 (1.05, 1.43), n=14,442	OR=1.61 (1.37, 1.89), n=4,774
Males, n=32,417	REF, n=12,356	OR=1.06 (0.89, 1.27), n=13,595	OR=1.27 (1.06, 1.52), n=6,466
Peltzer & Pengpid (2015)			
Females, n=3534	REF	OR=2.31 (1.51, 3.52)	OR=5.76 (3.84, 8.64)
Males, n=2846	REF	OR=1.19 (0.77, 1.85)	OR=3.94 (2.46, 6.32)

The blue shaded cells include statistically significant results for males and the pink cells for females. Kim & Kim (2010): ORs adjusted for age, family living structure, household economic status, academic performance, perceived body weight, unhealthy weight control behaviour, current alcohol drinking, current cigarette smoking, current butane gas or glue sniffing, subjective sleep satisfaction, and depressed mood. Peltzer & Pengpid (2015): ORs adjusted for age, psychological distress and current alcohol use.

3.3.3 Young adults

Summary:

One study found no significant direct relationship between total number of drinks per week or frequency of HED and attempted suicide over the following year in males, although an indirect relationship via depressive symptoms was reported.

A single case-control study was identified which included people who died by suicide (cases) or motor vehicle accident (controls). There was no difference between cases and controls on the likelihood of having alcohol in their bloodstream. However, there was a much higher rate of cases having a combination of alcohol and drugs in their toxicology results than in controls.

One study by Grazioli et al. (2018) reported on effect of alcohol consumption on suicide attempts in males. The risk of bias for this study is presented in Appendix D in the Technical Report. It had a moderate risk of bias for internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study, and a high risk of bias for generalisability to the broader population from which the study participants were selected. The study included 4,617 young men, aged 19–20 years, who attended army-recruitment centres. They measured the average number of drinking days and the number of standard drinks (=10 g of ethanol) consumed per drinking day over the past 12 months at baseline. They defined HED as consuming 60 g or more of pure alcohol quickly on a single, discrete occasion. The authors found no significant bivariate Spearman rank-order correlation between males who drank at age 19 and attempted suicide at age

20 years (rho=0.01 for drinks/week and rho=0.00 for HED). However, using structural equation model regression analysis (adjusted for demographic covariates on mediators and suicide attempt at baseline) to model drinking, depressive symptoms and suicide, the authors reported that although alcohol use was not significantly related to suicide attempt, there was a significant negative indirect (mediated) effect through depressive symptoms, such that alcohol use was negatively associated with depressive symptoms, which were in turn positively related to suicide attempts (Figure 30). There is *no reliable evidence of an association* alcohol consumption or HED and suicide attempts in males (GRADE ⊕⊕⊖⊖).

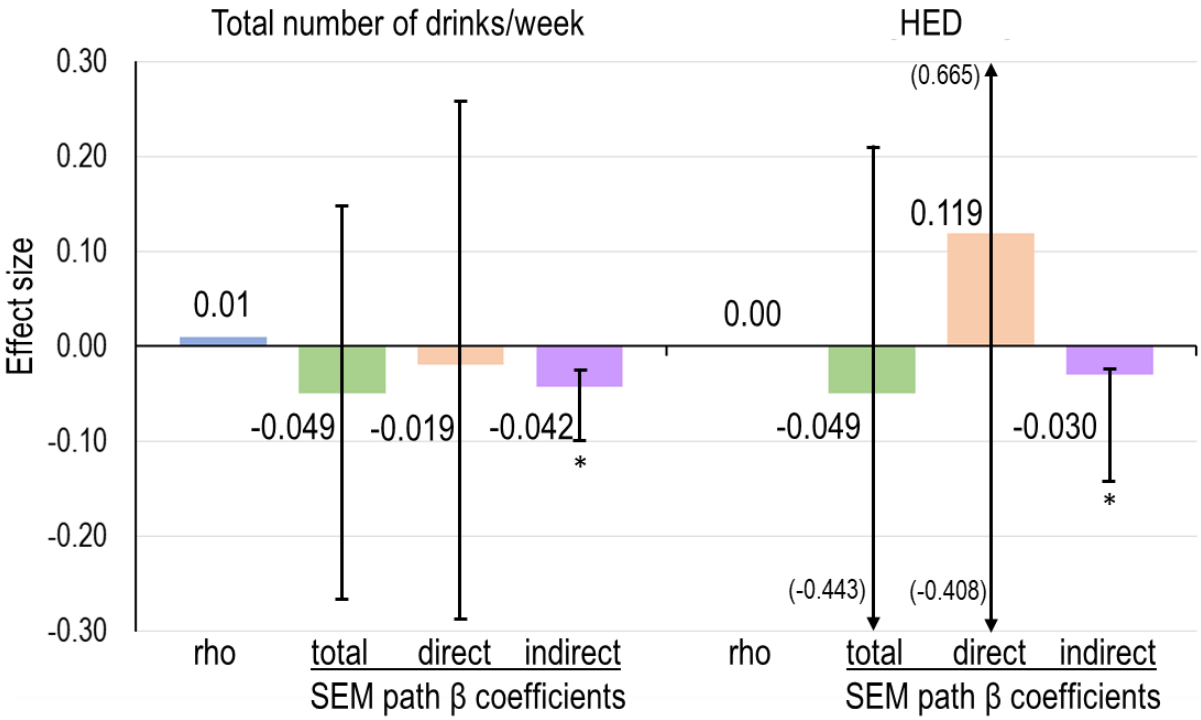

Figure 30 The association between drinking quantity or HED and suicide attempts within 12 months

Grazioli et al. (2018): Adjusted for demographic covariates on mediators and the main outcome (suicide attempt). SEM = structural equation modelling. The 95% CIs for the β coefficients are shown.

3.3.4 Adults

Summary:

Two studies assessed the association between alcohol consumption and suicide in an adult population.

One case-control study included people who died by suicide (cases) or motor vehicle accident (controls). There was no difference between cases and controls on the likelihood of having alcohol in their bloodstream. However, there was a much higher rate of cases having a combination of alcohol and drugs in their toxicology results than in controls.

A single cross-sectional study reported that amount of alcohol consumed per day (light to moderate vs heavy) was not associated with suicide thoughts and/or attempts after adjustments for confounding factors such as motives for drinking.

One case control study (Conner et al. 2017) of moderate internal validity and one cross-sectional study (Heberman Mash et al. 2016) with good internal validity reported on the association between alcohol and suicidality or completed suicide in an adult population.

The case-control study (level III-3 aetiological evidence) by Conner et al. (2017) reported on the involvement of alcohol in suicide victims compared to motor vehicle accident victims. It had a moderate risk of bias for both internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) and its generalisability to the broader population from which the study participants were selected. Alcohol and drug use were determined by toxicology reports. The presence of alcohol was based on BAC ≥ 0.001 g/dl, which is below the legal driving limit in Australia. The presence of 1 or more drugs including cocaine, opiate, amphetamine or methamphetamine was determined by a positive drug test result. Victims were grouped into 4 categories: those who tested positive for alcohol alone, for both alcohol and drugs, for drugs alone and for neither. Multivariate logistic regression analyses, using the neither group as the reference and adjusted for gender, age, and race/ethnicity, found that only those who had positive toxicology for both alcohol and drugs were more likely to have committed suicide that been in a car accident than those with a negative toxicology report (Figure 31).

Therefore, there is *no evidence of an association* between blood alcohol levels and suicide (GRADE ⊕⊖⊖⊖).

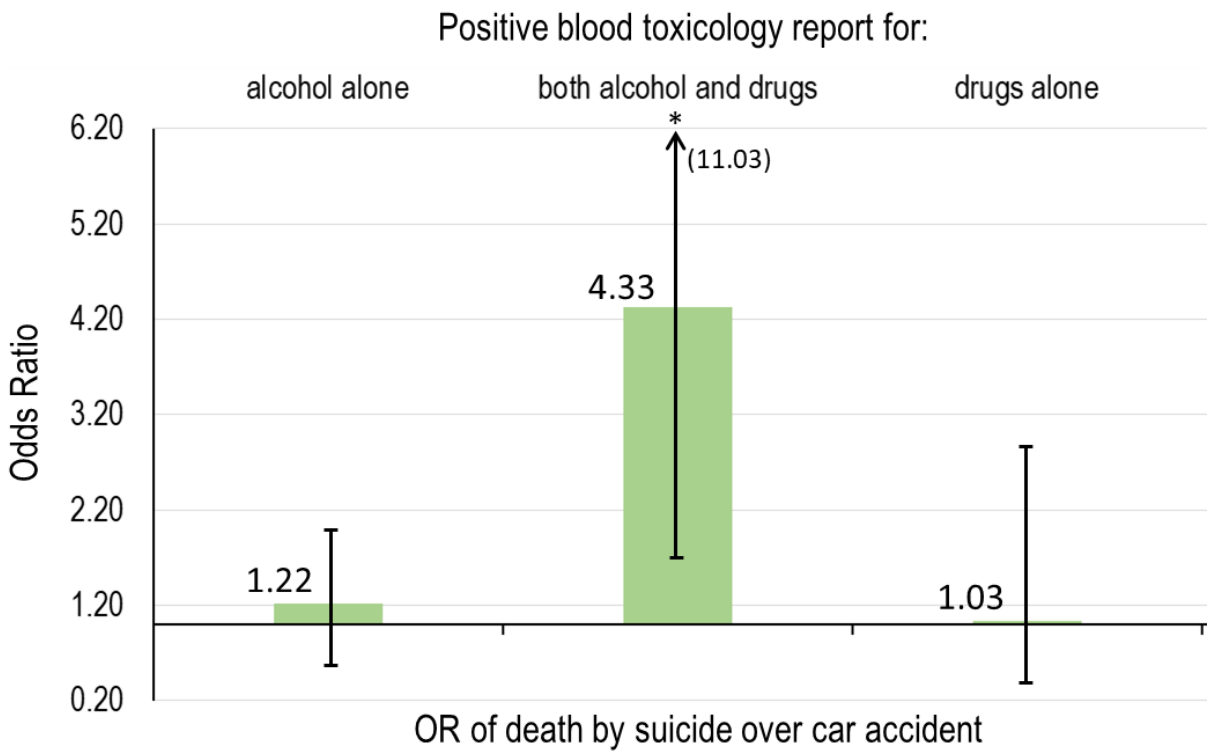

Figure 31 Bar graph depicting the OR (95% CI) for the likelihood of dying by suicide compared with a motor vehicle accident, if blood toxicology shows the presence of alcohol alone or in combination with another drug

The group with toxicology reports that were negative for both alcohol and drugs was used as the reference in logistic regression analysis. The green bars represent the OR and the 95% CIs are indicated by the line. Statistical significance is indicated by an asterisk. The ORs were adjusted for gender, age, and race/ethnicity. (Conner et al. (2017)

The cross-sectional study by Herberman Mash et al. (2016) assessed the average alcohol consumption per day (over the past month) and suicidality (whether the person had ever seriously considered or attempted suicide) in the past year in active duty military personnel who were lifetime alcohol users (87% male). In unadjusted analyses, those who drank heavily (at least 48.8 g

alcohol/day for men and 24.3 g alcohol/day for women) were significantly more likely to be suicidal than light/moderate drinkers (drinking less than the specified amounts. However, after adjustments for confounding factors such as level of depression or motives for drinking, heavy average alcohol consumption was no longer a significant predictor of suicidality (Figure 32). Nevertheless, motives for drinking did impact the relationship between drinking and suicidality. Those who drank to avoid rejection or to "fit in" were more likely to have seriously considered and/or attempted suicide than those who did not drink for this reason (OR=1.78, 95%CI 1.06, 3.00). Conversely, those who drank for pleasure/enjoyment had a non-significantly lower rate of suicidality than those who did not drink for this reason (OR-0.74, 95%CI 0.41, 1.32). There is *no reliable evidence of an association* between alcohol consumption and suicide thoughts or attempts (GRADE ⊕⊕⊖⊖).

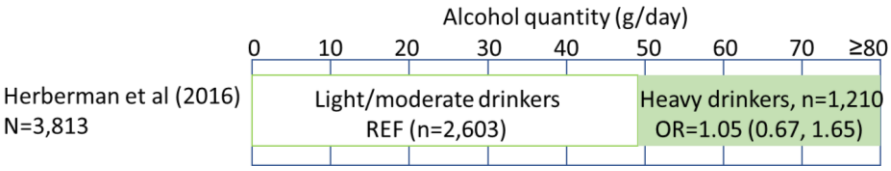

Figure 32 The association between suicidality within 3−8 years and the number of drinks consumed

The green bars represent the alcohol consumption categories in g/day. The 95% CIs are shown in brackets and the number of participants in each group are also shown. Lang et al. (2007): OR adjusted for age, gender, race, education, marital status, enlistment status, average daily alcohol use, depression, PTSD, avoid rejection/"fit in" motive, and pleasure-seeking./enjoyment motive.

3.4 The effect of alcohol consumption on anxiety and symptoms of anxiety (general population)

Eleven studies reported on the likelihood of developing anxiety as a consequence of alcohol intake. Four studies assessed the prospective relationship between alcohol consumption and anxiety in adult populations that also included older adults, six in an adolescent population and one in an older adult population. The risk of bias for these studies are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 33. Most studies had a low or moderate risk of bias for the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and for its generalisability to the broader population from which the study participants were selected.

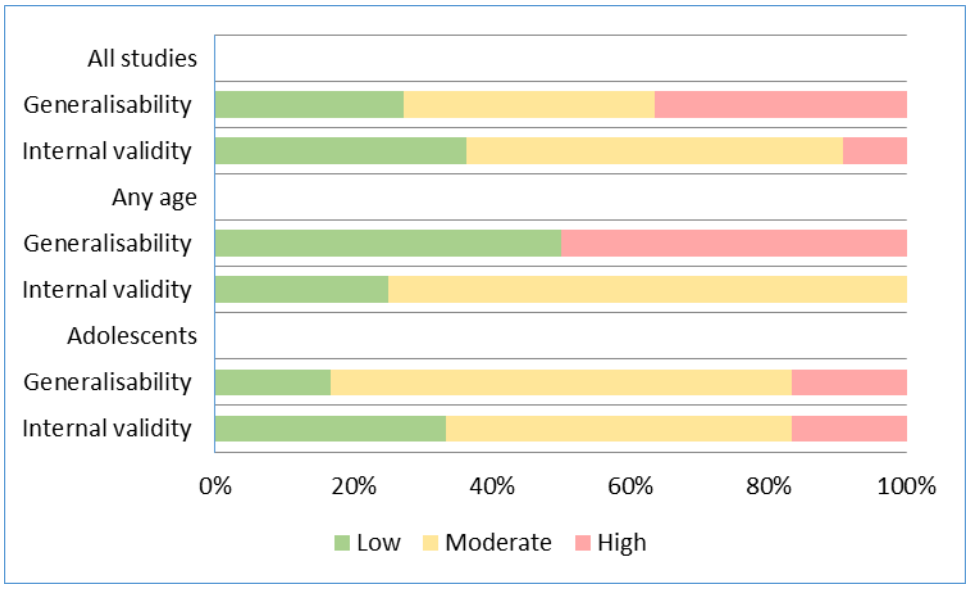

Figure 33 Risk of bias summary for studies reporting depression outcomes for individuals who drank alcohol
Eleven studies included results for any population, four included adults of any age and six included adolescents.

3.4.1 All ages

Summary:

Four articles from three studies reported on the association between alcohol and anxiety in general population cohort that included individuals of a wide age range.

Two of the articles included adults aged over 18 years from the NESARC study. Both studies adjusted for baseline levels of anxiety. One reported no significant differences in likelihood of developing anxiety by frequency of HED. The other found that those who drank less than weekly (or abstained), had higher levels of anxiety than those who drank alcohol on a weekly basis.

One study reported women who drank above guideline recommendations had significantly more likelihood of developing anxiety over the next 5-15 years than those who drank within guideline recommendations. However, there was no association between drinking above sensible drinking limits subsequent anxiety in men.

3.4.1.1 Combined sex/gender

The studies by Dawson et al. (2008) and Cougle et al. (2015) included adults aged over 18 years from the United States National Epidemiological Survey on Alcohol and Related Conditions (NESARC).

Dawson et al. (2008) had good internal validity and divided the cohort according frequency of risk drinking. Frequency of risk drinking was estimated as the number of days drinking ≥5 alcoholic drinks (70 g alcohol) for men and ≥4 alcoholic drinks (56 g alcohol) for women. The average age of the cohort was higher for never drinkers (47 years) and daily risk drinkers (42 years) than for the other risk groups (35−38 years). The authors found no difference in the odds of developing an anxiety disorder between those who never drank at high risk levels and any frequency of risk drinking (Table 30). There is *no evidence of an association* between HED frequency and developing anxiety (GRADE ⊕⊕⊕⊖).

Cougle et al. (2015) had moderate internal validity and divided the cohort into those who drank weekly and those who did not and found that those who consumed alcohol at least weekly had significantly less risk of developing anxiety than those who consumed it less than weekly. There is *limited evidence of an association* between weekly alcohol consumption and developing anxiety (GRADE ⊕⊕⊖⊖).

Table 30 Adjusted OR (95%CI) for the incidence of any anxiety disorder according to the frequency of risk drinking

	Never	<1/month	1−3/month	1−2/week	3−4/week	Daily/near daily
Dawson et al. (2008) N=22,122	REF	OR=1.03 (0.81, 1.31)	OR=1.13 (0.85, 1.51)	OR=1.09 (0.80, 1.48)	OR=1.43 (0.95, 2.13)	OR=1.31 (0.92, 1.88)
Cougle et al. (2015) N=43,093	REF (less than weekly)			Weekly alcohol consumption **OR=0.88 (0.82, 0.95), p<0.01**		

Dawson et al. (2008): OR adjusted for age, sex, race/ethnicity, whether married, whether employed, whether attended/completed college, health status, body mass index, tobacco use, drug use, any mood or anxiety disorder, any personality disorder, family history of alcoholism, volume of ethanol intake consumed on non-risk drinking days and mean quantity of drinks consumed on risk drinking days, and years since first drink. Cougle et al. (2015): OR adjusted for age, income, marital status, gender, ethnicity, education, and psychiatric comorbidity. Statistically significant result is shown in boldface.

3.4.1.2 Female and male subgroup analysis

Two studies with moderate internal validity reported on the likelihood of developing anxiety according to drinking quantity in women and one of these also reported outcomes for men.

An American study by Johnson et al. (2013) enrolled adult women who identify as lesbian and were aged 18-83 years, and reported that there was no association between hazardous drinking and anxiety four years later, after baseline levels of anxiety were taken into account (statistics not provided). This study was small (N=382), would have been underpowered to detect small differences.

A Danish study by Flensborg-Madsen et al. (2011) enrolled 18,146 adults aged ≥20 years who participated in the population-based Copenhagen City Heart Study. The authors divided the cohort into those who did not drink, those who drank within guidelines (0−14 drinks (0−168 g alcohol)/week for women and 0−21 drinks (0−252 g alcohol)/week for men), and those who drank above the guideline recommendations. The results have been converted to grams alcohol/day to be consistent with other studies and are shown graphically in Figure 34. The authors reported that women who consumed more than 24 g/day had a higher risk of developing anxiety compared to those who drank less and compared to those who abstained, but was not statistically significant in highest consumption group (≥36 g of alcohol/day). Therefore, there is *no reliable evidence of an association* between the quantity of alcohol consumed and anxiety in women. (GRADE ⨁⨁⊖⊖).

When all women who drank above guidelines (≥24 g/day) were compared with those who drank within the guideline recommendations, the women who drank more were twice as likely to develop anxiety up to 15 years later. There is *limited evidence of an association* between drinking above guideline recommendations and anxiety in women. (GRADE ⨁⨁⊖⊖).

This study also reported on this outcome for men and found that there was no association between drinking above sensible drinking limits of 36 g alcohol/day and subsequent anxiety over the next 5-15 years. There is *no reliable evidence of an association* between drinking above guideline recommendations and anxiety in men. (GRADE ⨁⨁⊖⊖).

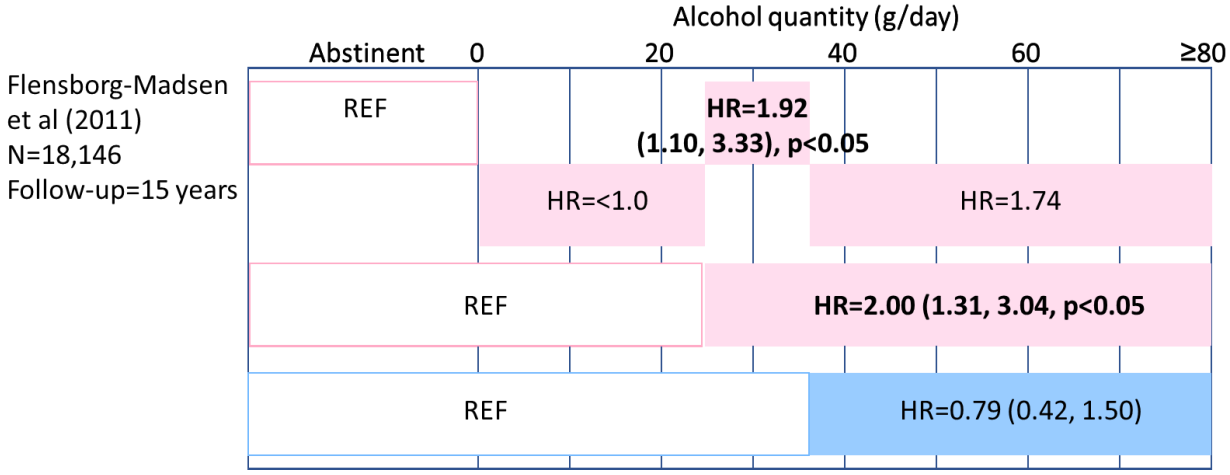

Figure 34 Graph depicting the HR (95% CI) for the likelihood of having anxiety among women according to their drinking quantity 15 years earlier compared with drinking no alcohol or drinking within guidelines

The pink bars represent the number of drinks/day included in each drinking category. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each drinking category was not reported. HRs are adjusted for smoking, co-habitation status, education, and income.

3.4.2 Adolescents

Summary:

Six studies assessed the impact of alcohol on anxiety levels in adolescents.

One study reported that neither weekly drinking nor drunkenness significantly predicted anxiety 2 years later. One study found no association between the frequency of alcohol drinking and anxiety symptoms 2 years later. Two studies reported on a combination of alcohol quantity per occasion by frequency of drinking and anxiety symptoms after 6 months to 3 years. One study, found no significant association. The other study measured alcohol use and anxiety every 6 months and had inconsistent results with some time-points being significant but the majority of time-points were not.

Two studies assessed the association between alcohol quantity and anxiety in adolescent males. One study reported a significant relationship between an increase in the average quantity of alcohol consumed per drinking occasion, and a higher risk of developing anxiety. This study reported that the impact was largest in 13-14 year olds. Another study found no association between occasional or weekly drinking and anxiety after 2 years in either males or females.

3.4.2.1 *Combined sex/gender*

Two studies reported on the prospective association between alcohol drinking frequency and anxiety in adolescents. One study, conducted in Finland, had moderate internal validity (Fröjd et al. 2011) and the other from the United Kingdom had good internal validity (Parrish et al. 2016). The results are tabulated in Table 31. Alcohol frequency was categorised by Fröjd et al. (2011) as a dichotomous variable (at least weekly drinking vs less than weekly), while Parrish et al. (2016) considered it as a continuous variable by taking the mean of the three drink types (beer, wine and spirits). Neither of these studies reported a significant association between alcohol frequency and the development of anxiety after 2 years. There is *no reliable evidence of an association* between drinking frequency and depression or depressive symptoms (GRADE ⊕⊕⊖⊖).

Table 31 Association between drinking frequency and anxiety in adolescents (combined sex/gender)

Study	Population	Exposure	Anxiety after 2 years
Fröjd et al. (2011)	15-16 year olds (N=2,070)	Drinking frequency Drinking ≥1-time/week compared with less than weekly drinking	OR=1.3 (0.6, 2.8)
Parrish et al. (2016)	14 year olds (N=620)	Drinking frequency	ß=0.02, NS

Fröjd et al. (2011): OR adjusted for gender, family structure, parental education and depression. Parrish et al. (2016): Adjusted for gender and generational status and delinquency.

Mackie et al. (2011) and Pardee et al. (2014) assessed alcohol consumption by multiplying the number of drinking occasions by the average number of drinks consumed per drinking occasion, over the last 6-12 months (Table 32). Mackie et al. (2011) had poor internal validity and measured

alcohol use and anxiety at four time-points 6 months apart. The authors reported two out of four cross-sectional correlations (alcohol and anxiety measures from the same time-point) as significant positive correlations and two out of six longitudinal correlations (alcohol measures taken at an earlier time-point compared to anxiety measures) as significant positive correlations (Figure 35). However, these correlations do not control for confounding factors, such as baseline levels of anxiety symptoms. Further analysis of the causal relationship between alcohol use and anxiety using SEM regression models found no significant directional effects between Q×F and anxiety (p>0.39; Table 32). Pardee et al. (2014) had moderate internal validity and did not find a significant association between alcohol use and the development of anxiety. However, they reported that a change in alcohol consumption levels was associated with a change in anxiety symptoms, with a slower than average decline of anxiety relating to more rapid increases in alcohol use. However, this result does not make it clear whether alcohol increases the risk of anxiety symptoms remaining high, or whether having high anxiety symptoms results in increases in alcohol consumption.

There is therefore *no reliable evidence of an association* between alcohol consumption in adolescence and subsequent levels of anxiety symptoms. (GRADE ⊕⊖⊖⊖)

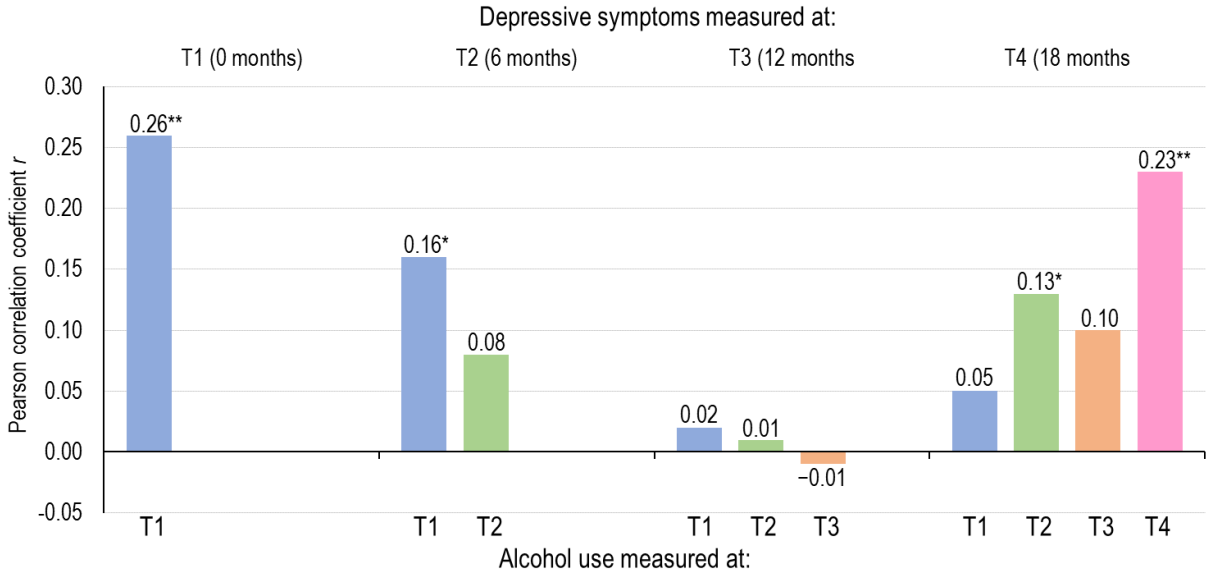

Figure 35 Bar graph depicting the Pearson correlation coefficient between alcohol consumption Q×F measured at age 14 (T1), then 6 (T2), 12 (T3) and 18 (T4) months later and anxiety at T1, T2, T3 and T4

The x-axis represents the wave at which alcohol use was assessed. Alcohol use was a composite of quantity and frequency. The blue bars represent alcohol measures taken from T1 (age 14 years). The green bars represent alcohol measures taken 6 months later. The orange bar represents alcohol measures taken at 12 months and the pink bar represents alcohol measures taken at 18 months. The time-point from which anxiety measures were taken is shown at the top of the graph. The asterisks indicates statistical significance (* p<0.05 and ** p<0.001). (Mackie et al. 2011)

Table 32 Association between quantity x frequency of alcohol and anxiety in adolescents (combined sex/gender)

Study	Population	Exposure	Outcome	Results
Mackie et al. (2011)	13 years old (N=393)	Quantity x frequency of alcohol	Anxiety after 6−18 months	SEM regression analysis showed no significant directional effects between Q×F and anxiety (p>0.39)
Pardee et al. (2014)	11-13 years olds (N=387)	Quantity x frequency of alcohol	Anxiety after 3 years	Alcohol intercept to general anxiety slope: *B*=0.001 Alcohol slope to general anxiety slope: *B*=0.012, p<0.05, *r*=0.14

The Finnish study with moderate internal validity by Fröjd et al. (2011) also reported on the association between drunkenness and anxiety. Frequent drunkenness was defined as at least weekly and was compared to those who were drunk less often. The authors reported no significant association between drunkenness and anxiety (Table 33). Therefore, there is *no reliable evidence of an association* between drunkenness in adolescence and subsequent anxiety (GRADE ⨁⨁⊖⊖).

Table 33 Association between drinking frequency and anxiety in adolescents (combined sex/gender)

Study	Population	Exposure	Anxiety after 2 years
Fröjd et al. (2011)	15-16 year olds (N=2,070)	Drunkenness Drunk at least once a week compared with less than weekly	OR=0.8 (0.2, 3.6)

Fröjd et al. (2011): OR adjusted for gender, family structure, parental education and depression.

3.4.2.2 *Female and male subgroup analysis*

One prospective cohort study with moderate internal validity from the United Kingdom reported the odds ratios (OR) and 95%CIs for the increased likelihood of adolescents aged 16 years developing anxiety according to their drinking frequency 1−3 years earlier, compared with little or no alcohol consumption (Edwards et al. 2014). The study did not report the cut-offs for low, medium or high drinking frequency, but defined them as none, occasional or weekly alcohol use over time between ages of 13 years to 15 years. The authors assessed the association between frequency of drinking (none, occasional or weekly) and anxiety in adolescent males and females (Figure 36). Teenage girls who reported weekly alcohol use had a significantly increased risk of having anxiety 2 years and 5 months later than those with low alcohol use (0R=1.78, 95%CI 1.13, 2.81). However, after adjusting for confounders such as housing tenure and conduct problems, there was no longer a significant relationship. There was no difference in the risk of anxiety among the different drinking categories for males (Figure 36). Therefore, there is *no reliable evidence of an association* between alcohol consumption and GAD in older adult males or females (GRADE ⨁⨁⊖⊖).

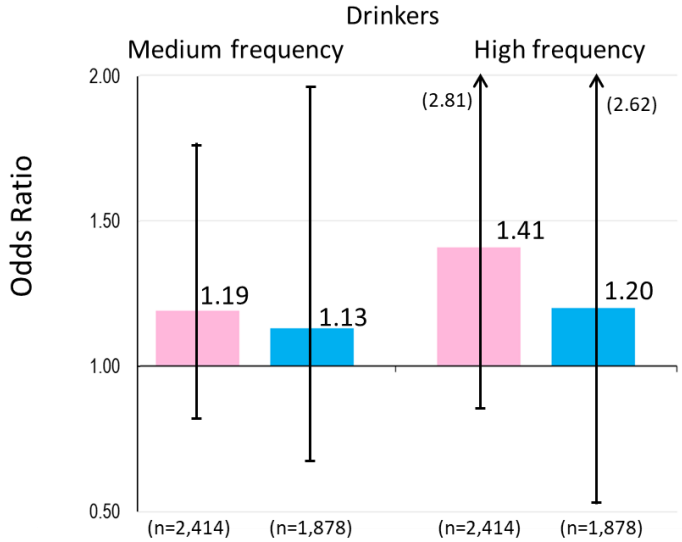

Figure 36 Bar graph depicting the OR (95% CI) for the likelihood of developing anxiety according drinking frequency 1−3 years earlier for male and female adolescents

The low alcohol use group was used as the reference in logistic regression analysis. The pink and blue bars represent the unadjusted ORs for females and males, respectively. The 95% CIs are shown as lines. The ORs for males were unadjusted. The ORs for females were adjusted for housing tenure (mortgaged/owned/ rented/subsidised rental), conduct problems at age 11, maternal depression factor score (Edwards et al. 2014)

A study conducted in the United States by Cerda et al. (2016) had good internal validity and reported on the association between alcohol drinking frequency or alcohol consumption quantity (per drinking session) and anxiety in male adolescents aged 13−19 years. The authors did not find a significant association between drinking frequency and anxiety, but did find an association between alcohol quantity per drinking session and anxiety. They reported that for each additional increase to the average number of drinks per occasion, the risk of developing an anxiety disorder increases by a small but statistically significant amount (an increase in their anxiety T-score of 0.12, 95%CI 0.05, 0.19). The effect was strongest in early adolescence (age 13-14), but was still statistically significant at ages 17-19 (Table 34). There is *limited evidence of an association* between the quantity of alcohol consume and anxiety symptoms in males (GRADE ⊕⊕⊖⊖).

Table 34 Association between frequency or quantity of alcohol and anxiety in male adolescents

Study	Population	Exposure	Follow-up	Results
Cerda et al. (2016)	N=503 male adolescents (aged 13-19 years)	Alcohol frequency:	per year	β=−0.00002 (95%CI −0.003, 0.003)
		Alcohol quantity	per year	β= 0.33 (95%CI 0.05, 0.61), p<0.05
		Alcohol quantity * age 13-14:	1 year	β=−0.36 (95%CI −0.62, −0.11), p<0.05
		Alcohol quantity * age 15-16	1 year	β=−0.26 (95%CI −0.84, 0.32)
		Alcohol quantity * age 17-19:	1 year	β=−0.20 (95%CI −0.38, −0.02), p<0.05

The green cells indicate statistically significant results

3.4.3 Older adults

Summary:

A single study in older adults reported no significant impact of frequency of HED on the likelihood of developing anxiety.

Only one study assessed the impact of alcohol consumption and anxiety in the subgroup of older adults. The American study by Chou, Liang & Mackenzie (2011) had a low risk of bias for the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) and a high risk of bias for its generalisability to the broader population from which the study participants were selected.

This study used data from the NESARC, focusing on middle aged and older adults (aged ≥50 years) and compared the likelihood developing generalised anxiety disorder (GAD) over 3 years according to HED (defines as ≥5 drinks (70 g alcohol)/session) frequency compared to non-HED. The results were graphed below according to the alcohol consumed per HED session (Figure 37). The authors reported that the point estimates for a HED frequency of less than once per month increased the likelihood of having GAD three years later compared with no HED by 28% in women and doubled the risk in men. Conversely, a HED frequency of at least once a month halved the likelihood of having GAD three years later compared with no HED in women and decreased the risk in men by only 12%. However, these findings were not statistically significant, most likely due to the small proportion of the study population who participated in HED.

Although the point estimates for abstinent women trended towards an increased risk of GAD and towards a decreased risk for men when compared to non-HED current drinkers, these differences were not statistically significant Therefore, there is *no reliable evidence of an association* between alcohol consumption and GAD in older adult males or females (GRADE ⊕⊕⊖⊖).

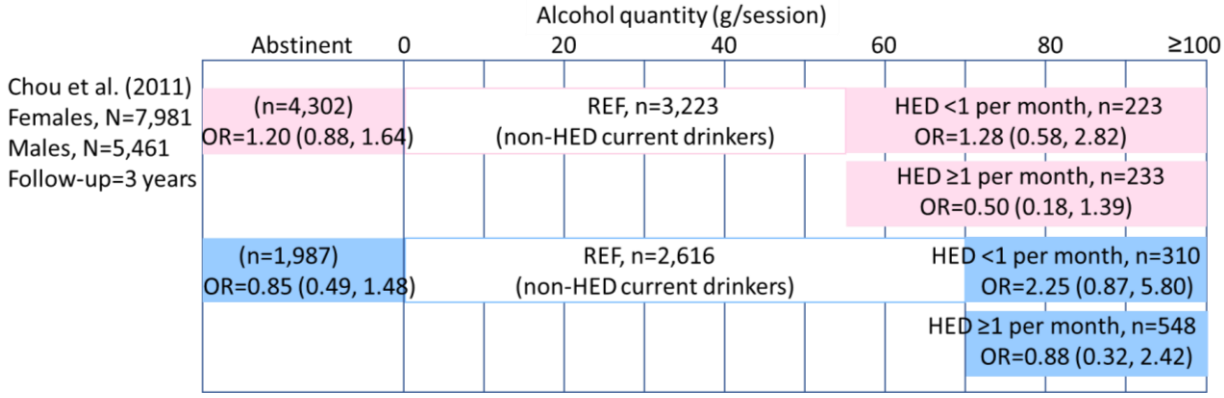

Figure 37 Graph depicting the OR (95% CI) for the likelihood of having GAD within 3 years among older women and men according to HED frequency

The pink and blue bars represent the number of drinks/session included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each drinking category are also shown. OR adjusted for age, marital status, education, race, household income, employment status, lifetime history of DSM-IV mood and anxiety disorders at Wave 1 assessment, and lifetime history of alcohol use disorder at Wave 1 assessment.

3.5 The effect of alcohol consumption on PTSD

Summary:

Three studies assessed the impact of alcohol on the likelihood of developing PTSD in the general population. In adolescents, the frequency of HED predicted PTSD after multiple imputations for missing data. In young adults, the association between drinking and PTSD was complex. Those who drank any alcohol, were more likely to have a change in levels of PTSD symptoms than non-drinkers, but drinkers were just as likely to have an improvement in symptoms as they were a worsening of symptoms. In older adults (aged ≥50 years), HED was only associated with PTSD in females.

Three longitudinal cohort studies reported on the likelihood of developing PTSD as a consequence of alcohol intake. Two prospective cohort studies from the United States reported on the association of HED and subsequent PTSD in national surveys (rather than focusing on groups of people exposed to trauma)[6]. The subpopulations included in the two studies reporting results from national surveys differed; one study with good internal validity but poor generalisability by Chou, Liang & Mackenzie (2011) included middle aged and older adults (aged ≥50 years) and a study with moderate internal validity and moderate generalisability by Cisler et al. (2012) included adolescents aged 12−17 years. A third study with a high risk of bias by Read et al. (2016), also from the United States, reported on the likelihood of having PTSD 5 months after assessment in young adults (college students with a mean age of 18 years) who were drinkers compared with non-drinkers (based on past month alcohol consumption).

In individuals with existing mental and physical illnesses. One study included people with depression, three studies included people with bipolar disorder and two studies included people with HIV. The risk of bias for these studies are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 41. The studies had a low or moderate risk of bias for the internal validity (i.e. the study design, data analysis methodology and adjusting for potential

[6] For PTSD in those exposed to trauma, see Section 4.5

confounders) of the study, and for the generalisability to the broader population from which the study participants were selected.

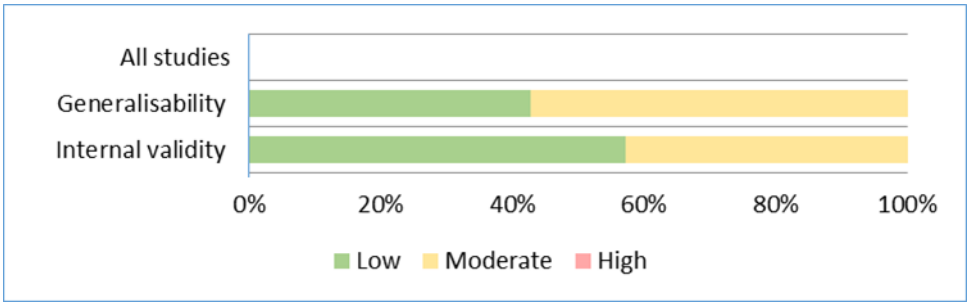

Figure 38 Risk of bias summary for studies reporting depression outcomes for individuals with existing mental and physical illnesses who drank alcohol

Three studies included results for people with depression, three studies included results people with bipolar disorder and two studies included results for people with HIV.

3.5.1 Adolescents

Cisler et al. (2012) had moderate internal validity and reported that the frequency of HED (defined as ≥5 drinks or 70 g alcohol/session) as a continuous variable and after multiple imputations for missing data, did not predict PTSD symptoms at a mean of 15 months later (Table 35). However, it did predict PTSD symptoms at a mean of 30 months later. The multiple regression analysis was adjusted for ethnicity, sex, age, interpersonal violence, baseline PTSD, delinquency, baseline depression. There is *limited evidence of an association* between alcohol consumption and PTSD in young adults (GRADE ⊕⊖⊖⊖).

Table 35 Association between frequency of HED and PTSD in adolescents

	At T2 (mean 15.3 months)	At T3 (29.7 months)
HED at T1	β=0.02, t=1.01	β=0.14, t=2.20, p<0.05

Multiple regression analyses adjusted for ethnicity, sex, age, interpersonal violence, baseline PTSD, delinquency, baseline depression (Cisler et al. 2012)

3.5.2 Young adults

The study by Read et al. (2016) divided the young adult college cohort into three groups according to PTSD severity (severe, moderate or no PTSD symptoms). The authors then reported on the likelihood of changing PTSD symptom class in drinkers compared with non-drinkers (defined as no alcohol in the past 6 month) after 3 months (T1−T2) and after 4 months (T2−T3). The authors found that drinking alcohol was associated with both an increase and decrease in PTSD symptoms, especially in those with moderate PTSD (Figure 39). Being a drinker was associated with a reduced likelihood of transitioning from no symptoms to severe symptoms, and conversely with an increased likelihood of transitioning from severe symptoms to no symptoms. However, the significance of these results are unknown as no confidence intervals or p-values were reported. Therefore, there is *no reliable evidence of an association* between alcohol consumption and PTSD in young adults (GRADE ⊕⊖⊖⊖).

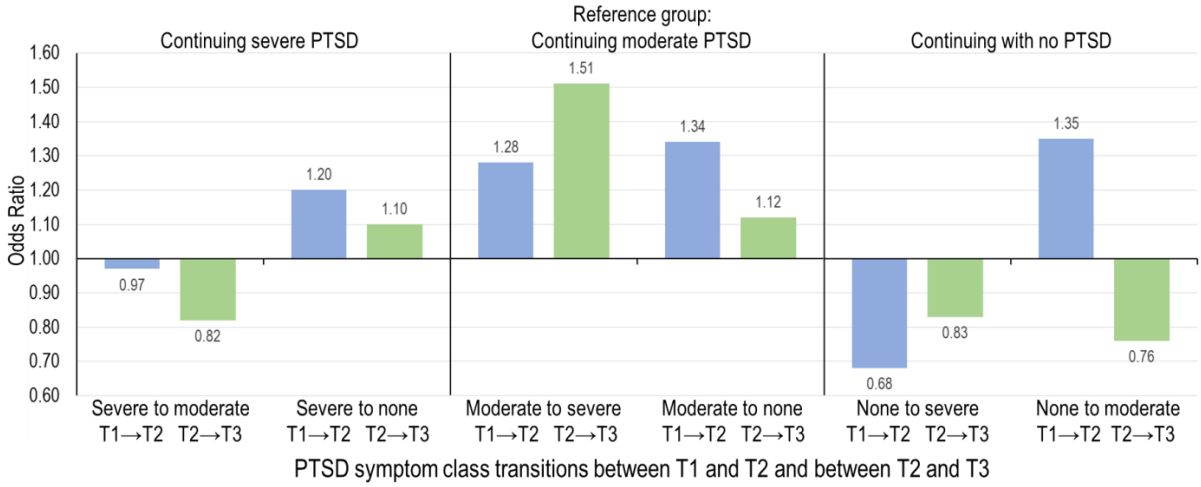

Figure 39 Graph depicting the OR for the likelihood of changing PTSD status over 7 months among young adult college students

Read et al. (2016). The blue bars represent the odds of changing PTSD status in drinkers compared to non-drinkers in a 3-month period between September and December (T1→T2), and the green bars in a 4-month period between December and April (T2→T3).

3.5.3 Older adults

Chou, Liang & Mackenzie (2011) compared the likelihood developing PTSD over 3 years according to HED (defines as ≥5 drinks (70 g alcohol)/session) frequency compared to non-HED, in middle aged or older adults (aged ≥50 years). The authors reported that older women with a HED frequency of less than once per month had over 2.5 times the odds of developing PTSD 3 years later compared with non-HED current drinkers (Figure 40). There is *limited evidence of an association* between HED and PTSD in women (GRADE ⨁⨁⊖⊖).

No significant result was observed in males. There is *no evidence of an association* between HED and PTSD in women (GRADE ⨁⨁⊖⊖).

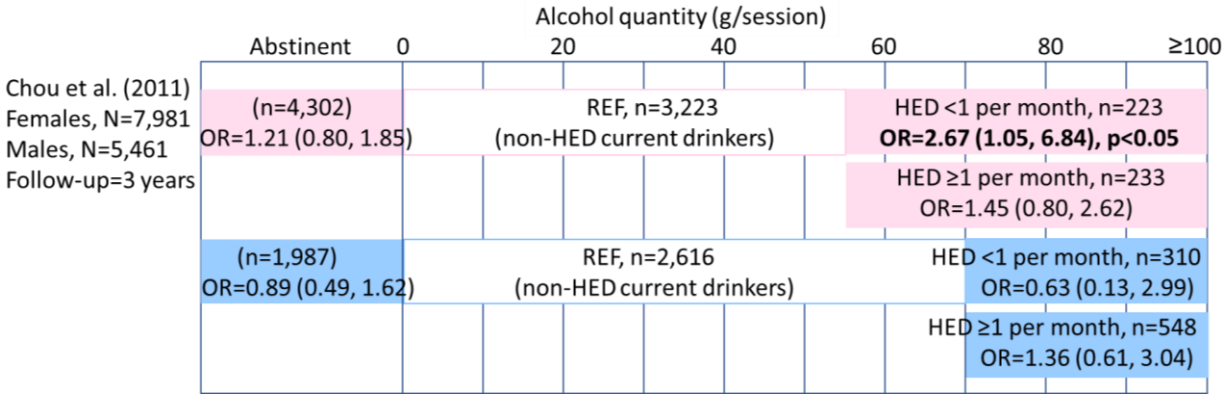

Figure 40 Graph depicting the OR (95% CI) for the likelihood of having PTSD within 3 years among older women and men according to HED frequency

The pink and blue bars represent the number of drinks/session included in each drinking category for females and males, respectively. The 95% CIs are shown in brackets and statistically significant results are shown in boldface. The number of participants in each drinking category are also shown. OR adjusted for age, marital status, education, race, household income, employment status, lifetime history of DSM-IV mood and anxiety disorders at Wave 1 assessment, and lifetime history of alcohol use disorder at Wave 1 assessment.

3.6 The effect of alcohol consumption on alcohol-related psychoses (general population)

No studies were identified which reported on the risk of alcohol-induced psychosis resulting from alcohol consumption.

4 Results – other subgroups

4.1 People with existing mental and physical illnesses

Summary:

Seven studies which focused on people with unipolar depression, bipolar depression or people with HIV were included for the subgroup of 'people with existing mental and physical illnesses.

One small studies in adolescents with unipolar depression reported that HED halved the chance of remission from depression over the study period. There was no significant difference between regular and occasional drinkers. There was also no significant difference between any of the drinking categories for recovery from depression.

Three small studies focused on the influence of alcohol on the course of bipolar depression. One study reported that any alcohol consumption in one quarter predicted a depressive episode in the following quarter. Similarly, a second study reported that each additional day of alcohol use in a month, increased the chances of a depressive episode in the following month by 3%. The third study was inconsistent, reporting no association between alcohol and depressive episodes in males or females with bipolar disorder. It did, however, report that alcohol use was associated with a transition from euthymia to mania in males, and from depression to euthymia in females.

Two studies in people with or without HIV investigated the influence of alcohol on depression. The larger study reported that HED increases of the odds of depression by over 2.5 times compared to those who drank at levels which were not considered hazardous, but there was no difference in the likelihood of depression due to HED between those with and without HIV. The second small study, with a high proportion of abstainers, reported that CES-D scores increased as drinking quantity increased with HED having in the highest scores but the differences were not statistically significant.

Seven longitudinal cohort studies reported on the likelihood of developing depressive symptoms, having a depressive episode, contemplating suicide or a change in mood related to bipolar disease as a consequence of alcohol intake in individuals with existing mental and physical illnesses. One study included people with depression and reported on the likelihood of remission or recovery according to alcohol intake. Three studies included people with bipolar disorder reported on the likelihood of having a depressive episode or a change in mood according to alcohol use; two used the number of drinking days per month and one reported on any versus no alcohol use. Three studies included people with HIV, two reported on the association between alcohol and depression and one on alcohol and suicidal ideation. The risk of bias for these studies are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 41. All studies had a low or moderate risk of bias for the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study, and only one study had a high risk of bias for the generalisability to the broader population from which the study participants were selected (Sullivan et al. 2008).

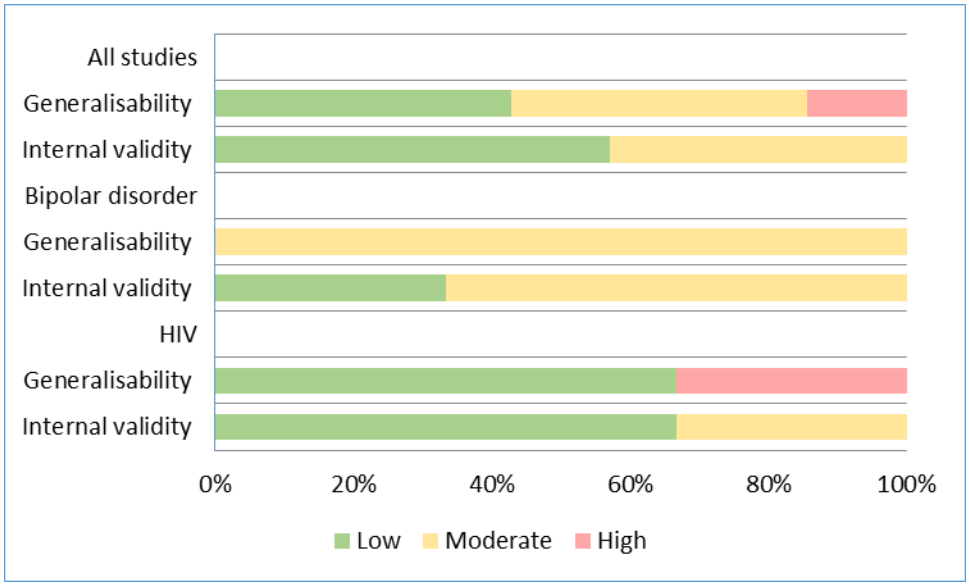

Figure 41 Risk of bias summary for studies reporting depression outcomes for individuals with existing mental and physical illnesses who drank alcohol

Seven studies included results for people with existing mental and physical illnesses, depression, three studies included results people with bipolar disorder and two studies included results for people with HIV.

4.1.1 Unipolar depressive mood disorders

Studies which assessed how alcohol consumption levels influenced response to treatment for depression were not included in this systematic review. However, one study by Meririnne et al. (2010), with good internal validity, was identified which reported on the influence of HED on outcomes of depression, in a naturalistic treatment setting (Table 36). The 197 adolescents had a depressive mood disorder at baseline and 13% had a baseline substance use disorder. Excessive drinking was defined as weekly drunkenness, or consuming typically more than 7 drinks (84 g alcohol) for females or 10 drinks (120 g alcohol) for males per session. Regular drinking was defined as less than weekly drinking and no/occasional drinking as abstinence or less than monthly drinking.

Those who were drank excessively at baseline were significantly less likely to experience remission of their depressive episode in the following year than those who either abstained or only drank occasionally (Table 36). However, excessive or regular drinking did not predict sustained recovery from depressive symptoms compared to no/occasional drinkers.

There is therefore *limited evidence of an association* between HED and continuing depression in adolescents with unipolar depression (GRADE ⊕⊕⊖⊖).

Table 36 The association between alcohol consumption and remission/recovery from depression, in adolescents with depression at baseline.

	No/occasional use (less than monthly non-excessive drinking) (n=81)	**Regular use** (less than weekly non-excessive drinking) (n=81)	**Excessive use** ≥84 g (women) ≥120 g (men) alcohol/session (n=35)
Remission from depression	REF	HR=1.02 (0.71, 1.47)	HR=0.49 (0.27, 0.89), p=0.020
Recovery from depression		OR=1.28 (0.63, 2.59)	OR=0.96 (0.35, 2.66)

The 95% CIs are shown in brackets and the green cells indicate a statistically significant result. The number of participants in each drinking category are also shown. HR = hazard ratio; OR = odds ratio; REF = reference group. Source: Meririnne et al. (2010)

4.1.2 Bipolar disorder

Three small prospective cohort studies assessed the impact of alcohol consumption on mood states in people with bipolar disorder. The three studies reported on depressive or manic outcomes according to any alcohol use versus no alcohol use, changes in frequency of any alcohol use or heavy alcohol use and changes in quantity of alcohol consumption. The results are summarised in (Table 38).

4.1.2.1 Combined gender

Baethge et al. (2008), had good internal validity, and defined the consumption of alcohol as either present or absent, and along with the presence or absence of depressive or manic symptoms were dichotomised, regardless of severity for analysis using GEE-based, population-averaged, regression models adjusted for age, sex and exposure-time (Table 38). Of the included bipolar patients, 45.2% met DSM-IV criteria for a substance use disorder with alcohol being the most common. The mean follow-up was 4.7 years, during which subjects experienced a mean of 1.6±1.1 DSM-IV major affective episodes/person/year. The authors reported that consumption of alcohol (of any volume) increased the chances of a depressive episode in the following quarter.

The study by Jaffee et al. (2009) had moderate internal validity, and reported on the odds of having a depressive episode per additional day of any alcohol use or heavy alcohol use in the past month among bipolar patients. Most patients 57% had both drug and alcohol dependence, 32% had alcohol dependence only, and 10% had drug dependence only. Heavy alcohol use was defined as ≥3 dinks or 42 g alcohol on any one day. The authors reported that each day of any alcohol use in the past month, increased the odds of depression in the following month by 3.6% and by 3.3% for each additional day of alcohol use (Table 38). For each 10-days of use, the odds increased by 42.1% and 2.3-times for each additional 10 days of alcohol use. The increases were greater for heavy alcohol use, with a 4.2% increase in the chances of depression per day of heavy alcohol use and 1.5-times increase per 10 days of heavy alcohol use.

The small sample sizes, combined with the heterogeneity of results, mean that the overall level of association between alcohol consumption, and mental health outcomes in patients with bipolar disorder, cannot be determined. Therefore, there is *no reliable evidence of an association* between alcohol consumption and risk of different mood states in people with bipolar disorder (GRADE ⨁⊖⊖⊖).

Table 37 The association between alcohol consumption and different mood states in people with bipolar disorder

	Mania or hypomania	Depression
Baethge et al. (2008) N=166	β=−0.014 to 0.011 z-scores −0.74 to 0.64 p=0.046−0.59	β=0.058 (95%CI 0.015, 0.100) z-score 2.67; p=0.007
Jaffee et al. (2009) N=115		Per day of alcohol use OR=1.036 (1.010, 1.062) Per 10 days of alcohol use OR=1.421 (1.102, 1.832) Per day extra of alcohol use OR=1.088 (1.033, 1.146) Per 10 days extra of alcohol use OR=2.326 (1.380, 3.921) Per day heavy alcohol use OR=1.042 (1.010, 1.078)

		Per 10 days heavy alcohol use OR=1.527 (1.100, 2.119)

The 95% CIs are shown in brackets and green cells indicate statistically significant results. Baethge et al. (2008) Analysis was adjusted for age, sex and exposure-time.

4.1.2.2 Female and male subgroup analysis

The third study by van Zaane et al. (2014) with had moderate internal validity reported on results for men and women with bipolar disease separately, 44% of whom had alcohol dependence. The authors looked at the time to transition from one mood state to another, associated with an increase in weekly consumption of alcohol by one standard drink (10 g alcohol)/day. They reported that an increased consumption of 10 g alcohol per week had no influence on the time to transitioning to a depressive episode for either males or females. However, it was significantly related to a shorter transition from depression to euthymia in females and protective against a transition from euthymia to mania in males (Table 38).

The small sample sizes, combined with the heterogeneity of results, mean that the overall level of association between alcohol consumption, and mental health outcomes in patients with bipolar disorder, cannot be determined. There is therefore *no reliable evidence of an association* between alcohol consumption and risk of different mood states in people with bipolar disorder (GRADE ⨁⊖⊖⊖).

Table 38 The association between alcohol consumption and different mood states in people with bipolar disorder

N=137	Mania or hypomania	Euthymia	Depression
Males	Euthymia → Mania HR=0.81 (0.71, 0.92)	Depression → Euthymia HR=0.95 (0.90, 1.01)	Euthymia → Depression HR=1.03 (0.97, 1.11)
		Mania → Euthymia HR=0.94 (0.84, 1.05)	
Females	HR=1.01 (0.85, 1.18)	Depression → Euthymia HR=1.18 (1.03, 1.36)	Euthymia → Depression HR=0.97 (0.82, 1.14)
		Mania → Euthymia HR=1.12 (0.94, 1.34)	

The 95% CIs are shown in brackets. The blue cells indicate statistically significant results for males and the pink cells for females. (van Zaane et al. 2014)

4.1.3 HIV

4.1.3.1 Depression

Two studies by Sullivan et al. (2008; 2011) assessed the relationship between alcohol and depression or depressive symptoms in people with HIV, or including participants with or without HIV. The larger study with good internal validity by Sullivan et al. (2011) included 1,339 Veterans with HIV and 1,107 without HIV, and found that HED was independently associated with depression after adjusting for potential confounding; patients who participated in HED were twice as likely to develop depression compared with non-hazardous drinkers (defined as consuming alcohol in previous year but not a HED or hazardous drinker) (Figure 42). The authors also reported that HIV status did not significantly alter the relationship between drinking patterns and depression. Generalised estimating equation modelling found that the interaction between HED and HIV status was not statistically significant. There is *evidence of no association* between HED and depression at follow-up (GRADE ⨁⨁⨁⊖).

The earlier study with moderate internal validity, in which 58% of participants consumed no alcohol in the month prior, reported that depressive symptoms appeared to increase as drinking levels increased, with the highest values being for HED, but the differences were not statistically significant after adjustment for potential confounders (Figure 42). There is *evidence of no association* between HED or heavy drinking and depressive symptoms at follow-up (GRADE ⊕⊕⊕⊖).

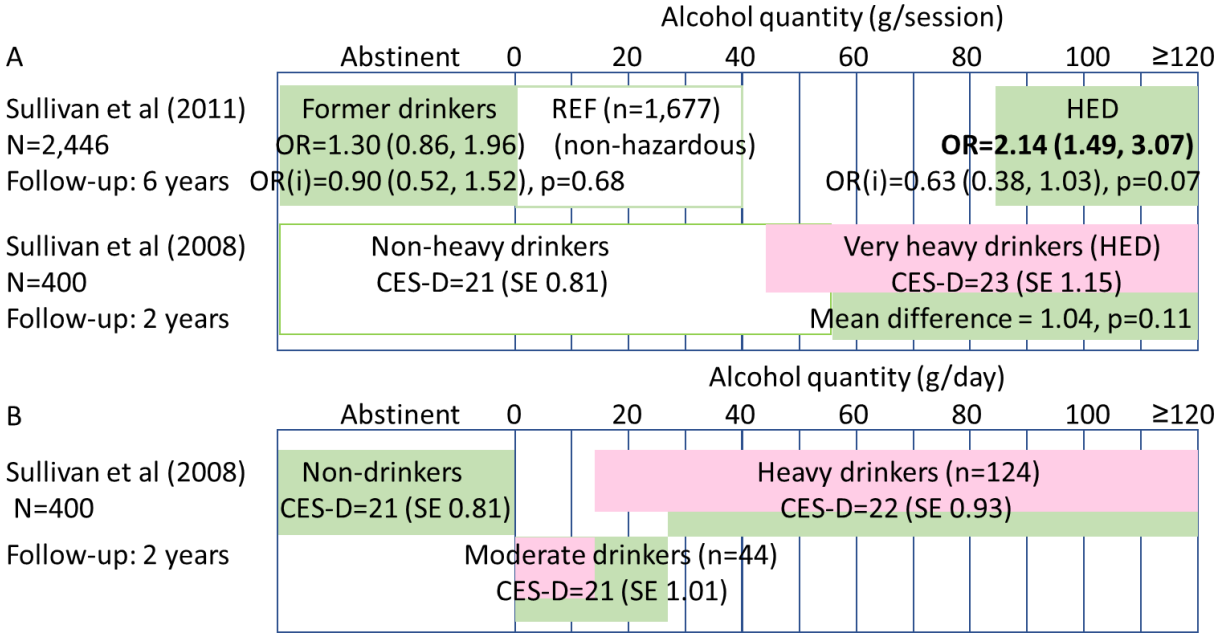

Figure 42 The association between developing depression within 4 years and the mean number of drinks consumed either per drinking session (A) or per day (B) among HIV positive individuals

Sullivan et al. (2011) used generalised estimating equation with ordinal alcohol consumption and MDD or depressive symptoms. The OR (95% CI) for depression in former drinkers and HED are shown, and the OR for interaction (i) with HIV status is shown directly underneath. Sullivan et al. (2008) compared the difference in CES-D score for different drinking categories. Mean differences were adjusted for gender, age, race/ethnicity, homelessness, hepatitis C virus antibody status, CD$ cell counts, human immunodeficiency virus log RNA measurements and time in months since study enrolment.

4.1.3.2 Suicidal ideation

One high quality cross-sectional study from the United States assessed how alcohol consumption, determined using the AUDIT-C, was associated with suicidal ideation (determined using a single item from the Patient Health Questionnaire, which focuses on the previous 2 weeks) in a HIV primary care setting (Lawrence et al. 2010). Although those who scored ≥5 on the AUDIT-C were almost twice as likely to report suicidal ideation than non-drinkers in unadjusted analyses (OR=1.96, 95%CI 1.23, 3.11), after adjustments for confounders such as age, race, level of depression and substance abuse, the level of alcohol consumption was no longer a statistically significant predictor of suicidality (Figure 43).

There was *no reliable evidence of an association* between high risk drinking and suicidal ideation at follow-up (GRADE ⊕⊖⊖⊖).

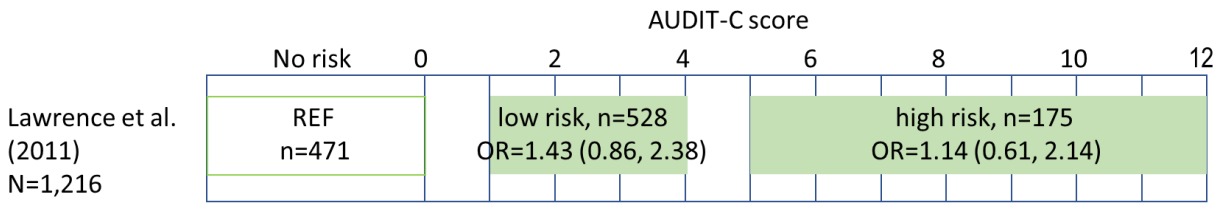

Figure 43 The association between AUDIT-C score and suicidal ideation among HIV positive individuals.

The 95% CIs are shown in brackets and the number of participants in each drinking category are also shown. OR adjusted for age, sex, race, insurance status, location, CD4 cell count, level of depression and substance abuse (Lawrence et al. 2011)

4.2 People with existing alcohol dependence

Although many studies were identified, which assessed the link between alcohol use disorder (AUD; including alcohol dependence and alcohol abuse) and mental health outcomes, no studies were identified which discussed the association between alcohol consumption and mental health outcomes, in people with AUD. The list of studies reporting on the link between AUD and mental health outcomes is available on request. A single study on people who were dependent on either alcohol *or drugs* is discussed in Section 4.4, page 86.

4.3 People with strong family history of alcohol dependence

No studies were identified that investigated the link between alcohol consumption and mental health outcomes in people with a strong family history of alcohol dependence. Some studies used family history as an independent variable, however, the interaction between this and alcohol consumption in the individual, and their effect on mental health outcomes were not assessed.

4.4 People on medicines or other drugs

Summary:

No studies were identified on the association between alcohol and mental health, focusing on people on medicines.

Three studies were identified which assessed how the combination of alcohol and other drugs was associated with depression and/or anxiety. Two studies reported that those who were heavy users of alcohol, cigarettes and marijuana were two to six times more likely to have a major depressive episode or anxiety disorder than those who only occasionally consumed alcohol. The third study was in people who were dependent on either alcohol or drugs, and reported that in this population, each additional hazardous drinking occasion in a month would increase the chances depression symptoms by 10% and anxiety symptoms by 9%.

Three studies assessed the prospective relationship between alcohol consumption and depression and/or anxiety in people on other drugs. The risk of bias for these three studies are presented for individual studies in Appendix D in the Technical Report and are summarised in Figure 44. One study had a high risk of bias for the internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study (Brook et al. 2014). Two studies had a high risk of bias for the generalisability to the broader population from which the study participants were selected (Bahorik et al. 2016; Brook et al. 2014).

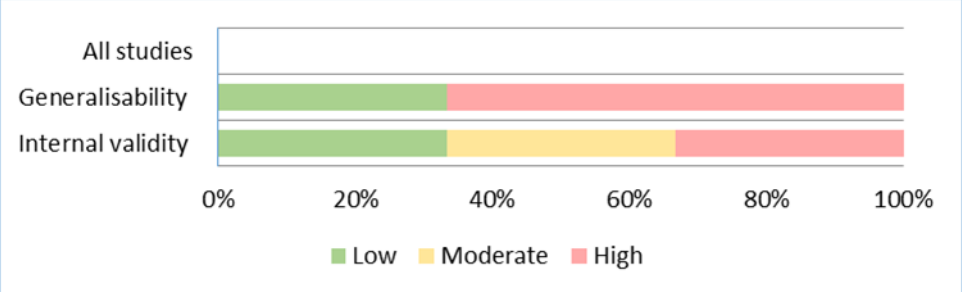

Figure 44 Risk of bias summary for studies reporting depression outcomes for individuals taking other drugs who drank alcohol

Three studies included results for this population.

Two studies by Brook et al. (2014; 2016) looked at the effect of a triple trajectory of alcohol consumption, cigarette use and marijuana use in adolescents on depression and/or GAD 13−23 years later (There was *limited evidence of an association* between hazardous drinking and depressive symptoms or anxiety symptoms at follow-up (GRADE ⊕⊕⊖⊖).

Table 39). Brook et al. (2016) divided the cohort into five groups; chronic, moderate-to-heavy cigarette, alcohol, and marijuana users, delayed/late-starting, moderate cigarette, alcohol, and marijuana users, little to no tobacco, moderate alcohol, and occasional marijuana users, chronic heavy smoking and moderate alcohol (but no marijuana) users and those who used only alcohol occasionally. They reported that compared to people who only occasionally consumed alcohol, only those who were chronic, moderate-to-heavy cigarette, alcohol, and marijuana users were statistically more likely (2.7-times) to have a major depressive episode. Thus, there was *limited evidence of an association* between use of all three substances in adolescents and depression over 23 years. (GRADE ⊕⊕⊖⊖).

Heavy use of all three substances increased the odds of a subsequent GAD by over 6 times compared with occasional alcohol consumption. Those who were in the moderate cigarette, alcohol, and marijuana use and the little to no tobacco use, moderate alcohol use, and occasional marijuana use groups were also 2.6 and 3.7-times more likely to have GAD than occasional alcohol consumers. Brook et al. (2014) divided the African American and Puerto Rican cohort into those who used: all 3 substances (tobacco, alcohol, and marijuana), marijuana and alcohol, tobacco and alcohol, alcohol only, and none. The authors reported that those who used all three substances were 4.4-times more likely to develop GAD than those who used none, and 2.2-times more likely than those who only drank alcohol. However, when those who used all 3 substances were compared to those who used alcohol in combination with either tobacco or marijuana, there was no longer any statistically significant difference between the groups. Thus, there is *limited evidence of an association* between use of all three substances and anxiety (13 to 23 years later). These studies were considered to have a moderate to high risk of bias, due to lack of adjusting for many confounding factors, and poor descriptions of the source populations or generalisability of the samples included.

There was *limited evidence of an association* between hazardous drinking and depressive symptoms or anxiety symptoms at follow-up (GRADE ⊕⊕⊖⊖).

Table 39 Association between alcohol consumption and other drugs (cigarettes and marijuana), and depression and anxiety

	Population	NON	LML	HMN	DDD	HHH
Depression						
Brook et al. (2016) Follow-up = 23 years	N=806 adolescents, mean age 14 years	REF	OR=1.92 (0.84, 4.41)	OR=1.10 (0.45, 2.69)	OR=0.85 (0.41, 1.76)	OR=2.67 (1.14, 6.26)
Anxiety						
Brook et al. (2016) Follow-up = 23 years	N=806 adolescents, mean age 14 years	REF	OR=3.71 (1.51, 9.10)	OR=1.70 (0.64, 4.55)	OR=2.64 (1.22, 5.75)	OR=6.39 (2.62, 15.56)
Brook et al. (2014)	N=816 urban AA	REF (none)			OR=4.35 (1.63, 11.63)	
			REF		OR=2.22 (1.33, 3.70)	

Follow-up = 13 years	and PR 20-year old participants		(alcohol only)		
				REF (tobacco and alcohol)	OR=1.53 (0.83, 2.80)
			REF (alcohol and marijuana)		OR=1.01 (0.56, 1.83)

HHH = chronic, moderate-to-heavy cigarette, alcohol, and marijuana use; DDD = delayed/late-starting, moderate cigarette, alcohol, and marijuana use; LML = little to no tobacco use, moderate alcohol use, and occasional marijuana use; HMN = chronic heavy smoking, moderate alcohol use but no marijuana use; NON = occasional alcohol use only. Brook et al. (2016): The green cells indicate statistically significant results. ORs adjusted for gender, age at T2, original residency in Albany county, T2 parental education level and T2 family income. Brook et al. (2014): ORs adjusted for gender, race/ethnicity, self-deviance (T1), depressed mood (T1), poverty (T5), and educational level (T5).

One prospective cohort study with good internal validity from the Unites States focused on adults (N=307) who had either alcohol or drug problems, and were referred to a dependence recovery unit (Bahorik et al. 2016). The median number of hazardous drinking days in the month before study interviews at baseline was 1.0 (IQR 0-4). Their sample was not large enough to examine risky substance use other than alcohol, which meant that the other substances were not discussed in the article. For each additional hazardous drinking occasion per month (≥4 drinks (56 g alcohol)/day for women; ≥5 drinks (70 g alcohol)/day for men), it was reported that there was a 10% increase in depressive symptoms (Figure 45). Likewise, for every reduction in hazardous drinking occasion per month, there was a 10% reduction in depressive symptoms.

Results were similar for anxiety, with corresponding 9% increases and decreases of anxiety symptoms depending on hazardous drinking levels (Figure 45). There was *limited evidence of an association* between hazardous drinking and depressive symptoms or anxiety symptoms at follow-up (GRADE ⊕⊕⊖⊖).

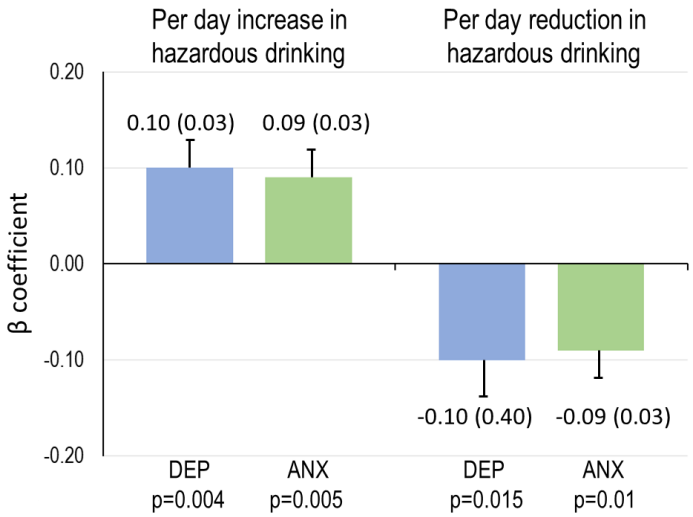

Figure 45 Association between increasing and decreasing alcohol consumption, and depression and anxiety in adults who had either alcohol or drug problems

Bahorik et al. (2016), the β coefficient (SE) and p-value are shown on the bar graph. The results for depression (DEP) are shown in blue and in green for anxiety (ANX).

4.5 The effect of alcohol consumption on people exposed to trauma

Summary:

Seven studies assessed the impact of alcohol on mental health in people exposed to various traumas.

PTSD

In people who have had traumatic injuries, one study reported that alcohol intake did not influence PTSD symptom severity and the second study found that blood alcohol concentration did not significantly predict PTSD symptoms 3 months later.

One study suggested that people who developed PTSD after the World Trade Center attack were more likely to report they drank more alcohol both prior to, and after, the attack. However, these results are potentially affected by recall bias.

Alcohol use was not found to influence rate of subsequent PTSD in two studies within Defence Force personnel or Veterans. However, one study noted that abstainers and heavy drinkers were significantly more likely to report PTSD at baseline than average drinkers.

No association remained between alcohol use at one time point and PTSD at a later time point for either women exposed to sexual assault or college students exposed to traumas, after adjustments were made for confounding factors.

Depression

One study reported that people with spinal cord injuries who reduced the frequency of HED after their injury had worse depressive symptoms at follow-up. This is hypothesised to be due to loss of social activities or social support rather than due to the change in alcohol consumption itself.

Seven prospective cohort studies provided evidence on the effect that alcohol consumption has on the risk of developing PTSD in people who have undergone a traumatic experience. Unfortunately, these studies could not be meta-analysed, due to heterogeneity in the method of analysing their results. Half of the studies reported a significant association between some measure of alcohol consumption and subsequent PTSD, PTSD symptoms, or change in PTSD symptom trajectory, while the other reported no statistically significant differences. One reason for differences in levels of PTSD may be the type of traumatic exposure. The results have therefore been divided into broad exposure type (traumatic injury; terrorism exposure; military populations, and mixed traumas (including sexual assault).

A small cross-sectional study was identified in the systematic review that reported very high prevalence rates of trauma exposure, PTSD, depression, anxiety, alcohol dependence and alcohol abuse among Australian Indigenous people (Nadew 2012). However, as this cross-sectional study did not report on the association between alcohol use and mental health disorders, it was excluded from this review. Nevertheless, it provides useful information about the Australian Indigenous population compared with the general Australian population and a summary of these comparisons are presented in Table 40.

Table 40 trauma and mental health rates comparison between the Australian Indigenous population included in the study by Nadew (2012) and the general Australian population

Disorder	This study	General Australian population
Trauma		
Any trauma	97.3%	
Physical attack (injured by violence)	40.7%	Males: 12.9%, females: 5.4%

Disorder	This study	General Australian population
Threatened with weapon	55.5%	Males: 16.5%, females: 7.0%
Rape	21.3%	Males: 0.6%, females 5.4%
Mental Health disorder		
PTSD	55.2%	1.3%
Major depression	22.2%	4.1%
General anxiety disorders	17.2%	2.7%
Alcohol dependence	33.5%	4.1%
Alcohol abuse	73.8	1.9

General Australian population averages from the Australian National Wellbeing and Mental Health Survey

In addition, one study with a low risk of bias for both internal validity and generalisability was identified that reported on depression in people who have undergone a traumatic experience.

The risk of bias for individual included studies are presented for individual studies in Appendix D in the Technical Report and the risk of bias for the studies reporting on PTSD outcomes are summarised in Figure 46. All studies had a moderate risk of bias for internal validity (i.e. the study design, data analysis methodology and adjusting for potential confounders) of the study and a low to moderate risk of bias for generalisability to the broader population from which the study participants were selected. Only one study had a high risk of bias for generalisability (Kaysen et al. 2011).

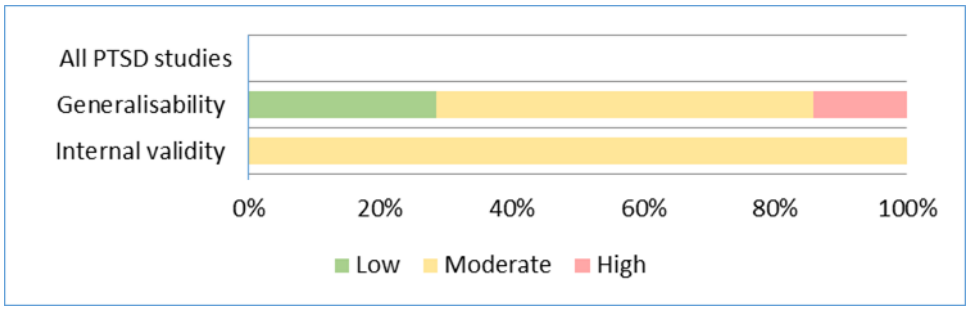

Figure 46 Risk of bias summary for studies reporting depression outcomes for individuals taking other drugs who drank alcohol

Seven studies included PTSD results for people exposed to trauma.

4.5.1 Alcohol and PTSD in populations exposed to trauma

Two prospective cohort studies with moderate internal validity and generalisability recruited patients who experienced a traumatic injury, asking about their alcohol consumption prior to the injury (Powers et al. 2014), or subsequent to injury (Hruska et al. 2017), and assessing the relationship between alcohol consumption and subsequent levels of PTSD symptoms.

Hruska et al. (2017) included adult patients at a Level I Trauma Centre and assessed the relationship between alcohol and PTSD symptom severity in a small (N=36) micro-longitudinal study (assessing both factors thrice daily over 7 days). Although fluctuations in PTSD symptom severity influenced alcohol intake, the reverse was not found, and alcohol intake did not influence PTSD symptom severity. However, within each person, greater alcohol consumption was related to greater concurrently reported PTSD symptom severity. This study was not powered to detect small differences.

Table 41 Association between alcohol consumption in the past week and PTSD after traumatic injury

N=36		Comparison
SF-PCL over 7 days	Alcohol consumption (from 0−≥140 g)	*B*=0.01 (95%CI −0.01, 0.02), NS
SF-PCL over 7 days	Alcohol consumption within each person	*B*=0.02 (95% CI 0.01, 0.03), p=0.005

The green cells indicate statistically significant results. OR adjusted for baseline PTSD symptoms (Hruska et al. 2017)

Powers et al. (2014) had moderate internal validity and also included adult patients at a Level I Trauma Centre. The authors measured the blood alcohol levels on admittance and reported that pre-trauma alcohol blood levels (either as a positive versus negative result, or as a continuous variable) did not predict PTSD 3 months later (Figure 47).

There is therefore *no reliable evidence of an association* between alcohol use and later PTSD symptom severity in people with traumatic injuries (GRADE ⨁⊖⊖⊖).

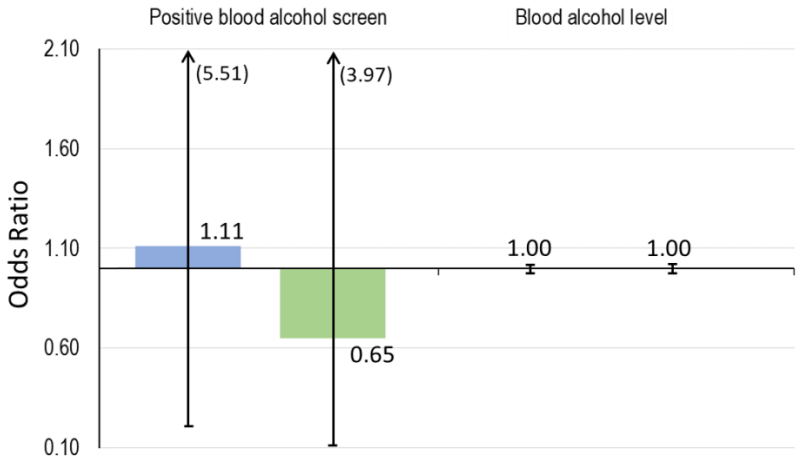

Figure 47 Bar graph depicting the OR (95% CI) for the likelihood of having PTSD at 3 months post-admittance to trauma centre according to blood alcohol level.

The blue bars represent unadjusted ORs. The green bars represent ORs that were adjusted for baseline PTSD symptoms. The 95% CIs are indicated. (Powers et al. 2014).

4.5.2 Alcohol and PTSD in populations exposed to terrorism

A single study with moderate internal validity and good generalisability reported on alcohol consumption before and following the World Trade Center attack in New York City, and the relationship between alcohol consumption and PTSD symptoms. Adults who were living in New York at the time of the attack were interviewed approximately 1 year later, and followed up after an additional year. Boscarino et al. (2011) reported that frequency of HED (≥6 drinks or 84 g alcohol/session), the number of drinks per drinking occasion, and the number of drinks per month all increased over time for those with later or delayed-onset PTSD, compared to those without (Figure 48). However, these results potentially allow for the self-medication model of PTSD symptom management. Alcohol use in the year prior and after the attack were determined retrospectively by asking participants about their drinking behaviour at 1 year following the attack. Although those who developed PTSD reported drinking significantly more in the year prior to and after the attacks than those who did not develop PTSD, it is unknown whether this is due to recall bias. There is therefore *no reliable evidence of an association* between alcohol consumption before or after terrorism-related trauma and subsequent PTSD (GRADE ⨁⊖⊖⊖).

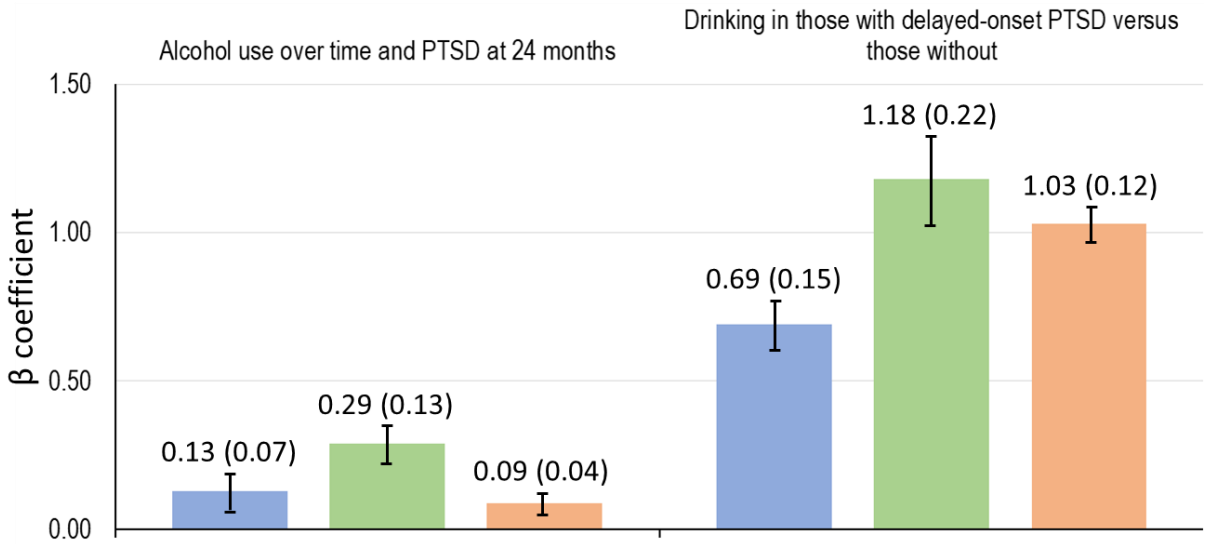

Figure 48 Association between alcohol consumption and PTSD at 24 months post-attack in those exposed to terrorism

The blue bars represent the number of drinks/month, green bars represent the number of drinks/drinking day and the orange bars represent HED. Boscarino et al. (2011): drinking outcomes were used as continuous variables and PTSD as a binary variable in generalized estimating equation analyses.

4.5.3 Alcohol and PTSD in Defence Force personnel or Veterans

Two studies with moderate internal validity and low-moderate generalisability assessed the link between alcohol consumption at one time point, and PTSD symptoms at a later time point, in military populations from either Australia, or the United Kingdom. It is unknown what proportion of participants would have met the criteria for undergoing traumatic events.

Goodwin et al. (2017) defined drinking categories from abstinence to heavy drinking as shown in Table 42 and noted that abstainers and heavy drinkers were significantly more likely to report PTSD at baseline than average drinkers. All drinking trajectory groups had more likelihood of probable PTSD at the first and second follow-ups (at 2–4 years and 5–7 years later) compared to average drinkers, although the differences were not statistically significant.

Schultz et al. (2014) used a cut-off of 3 on the AUDIT-C was used as a measure to identify patients with alcohol abuse, alcohol dependence or heavy drinking and was used as a binary variable, along with PTSD diagnosis, in logistic regression analysis. The authors did not find an association between alcohol consumption and PTSD 3 months later. However, the authors found that of all baseline demographics investigated, the lack of adequate deployment training was associated with worse PTSD symptoms.

There was *no reliable evidence of an association* between level of alcohol consumption prior to deployment, or post-deployment on later PTSD diagnosis or symptoms (GRADE ⊕⊖⊖⊖).

Table 42 Association between alcohol consumption and PTSD or PTSD symptoms

	Abstainers	Low-level drinkers	Average drinkers	Decreasing drinkers	Heavy drinkers
Goodwin et al. (2017)					
Number of participants in each group Weekly alcohol use (g)	n=29 0 g	n=124 Mean 16 g	n=366 Mean 144 g	n=18 Mean 88 g at baseline to 8 g at follow-up	n=127 Mean 224-232 g
Baseline	OR=14.89	OR=4.59		OR=10.02	OR=9.31

	(1.98, 111.62)	(0.75, 28.02)		(0.85, 117,98)	(1.77, 48.96)
Follow-up 2-4 years	OR=4.69 (0.70, 31.21)	OR=1.54 (0.47, 5.06)	REF	-	OR=1.60 (0.62, 4.14)
Follow-up: 5−7 years	OR=1.58 (0.19, 13.06)	OR=1.76 (0.57, 5.41)	REF	OR=2.15 (0.26, 18.20)	OR=2.68 (0.98, 7.33)
Schultz et al. (2014)					
Follow-up: 6 months N=512	REF				β=−0.04 (SD 0.13)

The green cells indicate statistically significant results. Goodwin et al. (2017): ORs adjusted for age and gender. Schultz et al. (2014): AUDIT-C score for heavy drinking, alcohol abuse or dependence and PCL-M scores for PTSD as binary variables in logistic regression analysis. Results adjusted for gender, age, ethnicity, education level, marital status, income, military status and branch, length of deployment, physical health, mental health, chronic pain, deployment risk factors and resilience factors.

4.5.4 Alcohol and PTSD in mixed traumas (in college students or women exposed to physical or sexual assault)

Two studies with moderate internal validity and moderate-poor generalisability were included in this section. Read et al. (2016) reported that trauma exposure is high in college students, with college attendance being a risk factor for some trauma types, such as sexual assault. Therefore this study has been grouped with a study by Kaysen et al. (2011) on women exposed to physical or sexual assault (Table 43). It should be noted that in the study by Read et al. (2014), the time between the traumatic event and study entry was not limited, and included childhood sexual assault, whereas the women included in the study by Kaysen et al. (2011) had all been assaulted within the past 5 weeks.

Although Read et al. (2014) reported a significant bivariate correlation between alcohol quantity at baseline and PTSD symptoms 1 year later in trauma-exposed college students, this association was not significant when entered into a cross-lagged structural equation (path) model. Kaysen et al. (2011) used hierarchical linear modelling for the course of PTSD symptoms over time and reported that the level of peak drinking (the highest amount of alcohol consumed in one day) in the 30 days prior to assault did not have any significant influence on PTSD symptoms at 5 weeks, 3 months or 6 months post assault, contrary to their hypothesis.

The two studies are therefore relatively consistent in that there is *no reliable evidence of an association* between alcohol consumption (prior to or after trauma) and later PTSD symptoms (GRADE ⊕⊖⊖⊖).

Table 43 Association between alcohol consumption and PTSD symptoms in trauma-exposed college students or female sexual or physical assault victims

Study and population	Time since trauma	Follow-up period		
		6 months	1 year	2 years
Read et al. (2014) N=734 trauma exposed students entering college	Any time		*r*=0.09, p<0.05	*r*=0.00
Kaysen et al. (2011) N=64 female sexual or physical assault victims	5 weeks	β=1.65 (95%CI −1.63, 4.93)		

The green cells indicate statistically significant results. Read et al. (2014): bivariate Pearson's coefficients, Kaysen et al. (2011): used hierarchical linear modelling with peak drinking level and PTSD symptoms as continuous variables.

4.5.5 Alcohol and depression in people exposed to trauma

One prospective cohort study assessed whether levels of alcohol consumption in people exposed to trauma, were associated with later incidence of MDD. In this study with good internal validity and generalisability, baseline alcohol consumption was measured one year after a spinal cord injury. In these patients, Hoffman et al. (2011) reported that those patients who reduced the level of their unsafe alcohol use between 1 and 5 years after their spinal cord injury, were 3 times more likely to be depressed 5-years after injury than those who never participated in unsafe alcohol use (Table 44). It is unknown whether cessation of alcohol use was associated with switching to more harmful drug use, or loss of social support (i.e. "drinking buddies").

There is *evidence of an association* between immediate post-trauma blood alcohol levels or post-trauma alcohol consumption and MDD (GRADE ⊕⊕⊕⊖).

Table 44 Association between alcohol consumption and MDD in patients with a spinal cord injury

	No unsafe use of alcohol	Reducing unsafe use	Beginning unsafe use	Continued unsafe use
Hoffman et al. (2011) N=1035 participants with spinal cord injuries	OR=1.0 (Reference)	OR=2.95 (95%CI 1.28, 6.79)	OR=1.47 (95%CI 0.62, 3.50)	OR=0.28 (95%CI 0.04, 2.18)

5 Discussion

A key strength of this systematic review is the number of large prospective cohort studies which were identified, which provided information on alcohol consumption or pattern of consumption at one time point, and then followed up to determine mental health outcomes at a later time point (or multiple time points). Prospective cohort studies are determined to be the highest level of evidence available for primary research on questions of aetiology (using the NHMRC levels of evidence hierarchy). However, although these studies provide information on the prospective association between alcohol and mental health, they are still not able to suggest causation. That is, although some studies show that high alcohol consumption is associated with a greater likelihood of depressive symptoms or anxiety at a later time point, the review cannot determine whether alcohol *causes* depressive symptoms or anxiety. They do not by themselves therefore clarify whether interventions to reduce or prevent alcohol intake improve mental health outcomes.

There were many examples where the identified studies were not consistent with each other. An example of this is whether low amounts of alcohol could actually be beneficial compared to abstinence in adults. Several studies did report that those who were abstinent were more likely to develop depression than those who drank a low to moderate amount of alcohol. However, there were other studies which reported either no significant difference, or reported a finding in the opposite direction. One possible reason for the differences are what factors are adjusted for. People may abstain from alcohol for a number of reasons, including religion, health reasons, economic reasons, and social reasons. It is unlikely that differences in depression between no alcohol and low to moderate amounts of alcohol are due to the direct effect of alcohol itself. Although most studies did try to adjust for confounding factors such as health status and socioeconomic status, it is still possible that underlying differences in the characteristics of drinkers versus abstainers were not able to adjusted for. In one study following patients who have had spinal cord injuries, a reduction in harmful drinking was associated with three times the chance of developing a major depressive disorder than those who never engaged in unsafe drinking (Hoffman et al. 2011). The authors hypothesise that those who reduce their drinking, may do so because of loss of social support or

social outlets. Likewise, McFarlane et al (2009) hypothesised that those who minimise alcohol use may be limiting their self-medication after a trauma.

Social support is a protective factor against depression (Santini et al. 2015), and in Australia, alcohol is considered integral to many social settings (Roche et al. 2009). Links between alcohol and mental health are therefore complex.

Limitations of the review

Cross-sectional results (other than for suicide) were not included in this review by themselves (i.e. unless in the context of correlations across the same and future time periods), as they may provide misleading results for the question about whether alcohol consumption influences mental health outcomes, by showing associations which may be due to effects in the opposite direction (i.e. poorer mental health may influence alcohol consumption, i.e. through self-medication). However, any results which were unadjusted for baseline mental health status, were also at risk of identifying associations between alcohol and mental health due to self-medication. This systematic review therefore preferences reporting of adjusted results, rather than unadjusted. Studies which reported correlations (most frequently presented in the analysis of depressive symptoms in adolescents), presented unadjusted results, so were at risk of suggesting a prospective relationship which may not exist.

Exposure levels (i.e. alcohol consumption level or pattern of drinking) were self-reported in all the studies. Self-reported alcohol consumption is at risk of social desirability bias, with individuals responding in socially desirable ways. This can lead to people under-estimating the amount or how often they drink (Davis, Thake & Vilhena 2010). Even in the context of online, confidential surveys (in which people generally feel more comfortable than in face-to-face, telephone or non-anonymous interviews), people who score high on 'impression management' consistently underreport their level of alcohol consumption (Davis, Thake & Vilhena 2010). Davis et al. (2010) reported a significant correlation between total AUDIT scores and impression management, such as those who scored high on impression management, reported lower AUDIT scores ($r(382)=-0.25$, $p>0.001$). The mean difference in AUDIT scores in the top third of distribution on impression management scores versus the bottom two-thirds on impression management was largest for heavy drinking, with high impression management people reporting approximately half as much hazardous drinking. Although it is possible that people who score high on impression management really do drink less, this explanation is thought unlikely (Davis, Thake & Vilhena 2010). Social desirability bias is therefore expected to reduce the accuracy of the exposure categories. With a decrease in accuracy of classifications, there is a reduced likelihood of finding associations between alcohol consumption levels and outcome measures.

It is possible that the exclusion of studies that used AUDIT to identify participants with alcohol abuse or alcohol dependence may have biased the study selection towards studies where the participants were lighter drinkers. Studies that reported on the differences between study participants and non-participants reported that, compared to participants, non-participants were more likely to be alcohol dependent (Armeli et al. 2015), be life-time alcohol users (Chan et al. 2013), have higher levels of alcohol use (Fröjd et al. 2011; Grazioli et al. 2018; Paulson et al. 2018) and have mothers who exhibited harmful drinking at child age 12 (Edwards et al. 2014). Several studies found no significant difference in the level of alcohol use between participants and non-participants (Cheng et al. 2016; Johnson et al. 2013, Paljärvi et al. 2009; van Zaane et al. 2014). Additionally, one study excluded people with heavy alcohol use at baseline (Chan et al. 2013), and conversely some studies excluded abstainers (Dawson et al. 2008; Grazioli et al. 2018; Paljärvi et al. 2009; Ruggles et al. 2017; Sullivan et al. 2011). Paljärvi et al. (2009) reflected that their reasons for abstaining were a probable source of unmeasured confounding.

Nearly all studies were classified as having at least some risk of bias, due to the possibility of self-report bias, the lack of adjustment for all relevant confounding factors, or poor description of the source populations and subsequent concerns about how generalizable the study population was to the source population.

Some studies, such as those in people exposed to trauma, were also at risk of recall bias. Some of the studies recruited participants who had been exposed to trauma, and asked them to recall how much alcohol they had consumed in the month or year prior to the trauma. It is possible that those who were more affected by the trauma may differentially recall the volume of alcohol consumption.

As with any systematic review, the integrity of the conclusions are threatened if publication bias is present (i.e. if the results published differ significantly from those which do not get published). Statistical methods have been developed to try and determine whether publication bias is likely or not. However, these methods are only relevant when multiple studies have been able to be meta-analysed. As the studies in this review were not able to be meta-analysed, standard procedures for determining publication bias were not able to be used. Trial registers were searched to see if there were any relevant studies which did not have a corresponding publication, however, no relevant prospective cohort studies were identified.

6 Assessment of the quality of evidence using GRADE

GRADE evidence profiles for people of all ages

Question: What is the effect of alcohol on mental health outcomes (across ages)?
Patient or population: General population (across youth and adults, males and females)
Exposure: Heavy drinking/excessive drinking/ drinking to exceed guidelines
Reference group: Abstinence/ non-hazardous

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=22,151 K=3 prospective cohort studies (Bulloch et al. 2012; Magnusson Hanson et al. 2016; Van Gool et al. 2007)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Excessive drinking (exceeding guidelines) vs abstinence or drinking within guidelines: RR=2.48 (1.05, 5.69), p<0.05, HR=0.9 (0.7, 1.3) ß=0.92, p>0.05 (n=193)	*No reliable evidence of an association* One out of three studies reported a statistically signficiant association between excessive drinking and an increased risk of depression.	Critical
	N=11,523 K=3 prospective cohort studies (Cabello et al. 2017; Van Gool et al. 2007) (Sullivan et al. 2011)	Risk of bias: -1 Inconsistency: 0 Indirectness: -1 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Non-heavy drinkers or regular (non-excessive) drinkers vs abstinence: OR=0.93 (0.57, 3.67) RR=1.15 (0.68, 1.96) Non-hazardous drinkers vs former drinkers: OR=1.3 (0.86, 1.96)	*No reliable evidence of an association* No relationship between regular drinking (not at hazardous levels) and depression 5-8 years later was found. Although these studies were consistent, a strong conclusion of no harm could not be made due to the risk of bias and the indirectness of the evidence (unclear how the drinking cultures in Ghana, Mexico, India and Russia differ from Australia).	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=27,630 K=3 prospective cohort studies (Bulloch et al. 2012; Cabello et al. 2017; Sullivan et al. 2011)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Heavy drinking on a given day and HED vs abstinent or drinking within guidelines: OR=1.59 (0.67, 3.75) HR=1.1 (0.9, 1.3) HED vs drinking within guidelines: OR=2.14 (1.49, 3.07), p<0.001	*No reliable evidence of an association* Only one out of three studies reported a significant relationship between HED (vs non-HED or abstinence) and a higher likelihood of depression or not after 5-8 years, although point estimates were in the same direction.	Critical
	N=37,092 K=3 prospective cohort studies (Cougle et al. 2015; Meng 2017a; Meng et al. 2017b)	Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Occasional or monthly drinkers vs never drinkers: RR=1.28 (1.12, 1.45) RRs=0.51 (0.44, 0.58) to 1.56 (0.61, 0.76) Monthly drinkers vs never or occasional drinkers: HR=0.88 (0.78, 0.995) Weekly drinker vs <weekly drinker: ORs=0.88 (0.83, 0.94) RRs=0.51 (0.44, 0.58) to 1.56 (0.61, 0.76)	*No reliable evidence of an association* Drinking weekly or monthly (not at hazardous levels) was found to be beneficial in three studies. Occasional drinkers had significantly higher levels of depression than never drinkers. No conclusions can therefore be made.	Critical
Bipolar disorder	N=43,093 K=1 prospective cohort study (Cougle et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0	⨁⨁⨀⨀	Weekly consumption vs less than weekly consumption: OR=0.79 (0.73, 0.86), p<0.001	*Limited evidence of an association* A single large study reported that those who drank less than weekly (or abstained), had higher levels of incident bipolar disease than those who drank alcohol on a weekly basis.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Large effect: 0 Confounding: 0				
Anxiety	N=22,122 K=1 prospective cohort study (Dawson, Li & Grant 2008)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Frequency of HED <1/month vs never: OR=1.03 (0.81, 1.31) 1-3/month vs never: OR=1.13 (0.85, 1.51) 1-2/week vs never: OR=1.09 (0.80, 1.48) 3-4/week vs never: OR=1.43 (0.95, 2.13) Daily/near daily vs never: OR=1.31 (0.92, 1.88)	*No evidence of an association* A single large study at low risk of bias found no significant differences in likelihood of developing anxiety by frequency of HED.	Critical
	N=43,093 K=1 prospective cohort study (Cougle et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Weekly consumption vs less than weekly consumption: OR=0.88 (0.82, 0.95), p<0.01	*Limited evidence of an association* A single large study reported that those who drank less than weekly (or abstained), had higher levels of anxiety than those who drank alcohol on a weekly basis.	Critical
Suicide	N=0 K=0				*No evidence for this outcome*	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0				*No evidence for this outcome*	Important

Question: What is the effect of alcohol on mental health outcomes (across ages)?
Patient or population: Females, general population (across youth and adults or younger adults and older adults)
Exposure: 5 drinks or over per week, or being monthly or weekly drinker
Reference group: less than 5 drinks per week, or never drinker

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=3,085 K=1 prospective cohort study (Sui et al. 2009)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨁⊖	≥5 vs <5 drinks per week (≥10 vs ≤10 grams per day): OR=1.00 (0.75, 1.33)	*The evidence shows no association* A single study at low risk of bias reported no difference in rates of depression between females who drank more or less than 10g of alcohol per day.	Critical.
	N=6,980 K=2 prospective cohort studies (Meng 2017a; Meng et al. 2017b)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Monthly drinker vs < monthly drinker: HR=0.92 (0.80, 1.05), Monthly drinker vs never drinker: RR=0.75 (0.63, 0.89) Occasional drinker vs never drinker: RR=1.49 (1.25, 1.77)	*No reliable evidence of an association* One out of two studies showed no association between drinking frequency on the rate of women developing depression at a later time point. One study reported that those who drank monthly had less chance of depression, while those drank occasionally had more chance of depression. The risk of bias, and inconsistency between results of Meng et al. 2017 means the certainty of evidence is very low.	Critical
Depressive symptoms	N=382 K=1 prospective cohort study (Johnson et al. 2013)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Hazardous drinking (≥84g alcohol/occasion) vs non-hazardous drinking or abstinence: β=0.18, p<0.05	*Limited evidence of an association* A single small study reported a positive association between hazardous drinking and depressive symptoms after 4 years. The evidence was rated down due to imprecision and a moderate threat to internal validity in the study.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Suicidal ideation	N=62,790 K=1 cross-sectional study (Glasheen et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	HED vs no HED and suicidal ideation athe same time point: OR=1.94 (1.74, 2.16)	*Limited evidence of an association* A single cross sectional study reported that HED was significantly associated with suicidal ideation in unadjusted analyses.	Important
Suicide attempts	N=62,790 K=1 cross-sectional study (Glasheen et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	HED vs no HED and suicidal attempt athe same time point: OR=2.77 (2.12, 3.61)	*Limited evidence of an association* A single cross sectional study reported that women (with or without MDE) who participated in HED were over twice as likely to attempt suicide compared with those who did not participate in HED.	Important
				Interaction between MDE and HED and suicide attempt Adjusted Wald χ^2=14.58(1), p<0.001).	*Limited evidence of an association* In those without MDE, participating in HED significantly increased the likelihood of attempted suicide, whereas in those with MDE, HED did not increase the risk.	Important
Anxiety	N=18,146 for males and females (N not stated by sex) K=1 prospective cohort study (Flensborg-Madsen et al. 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Alcohol quantity per day vs abstinence 0-24 g/day: HR=<1.0 >24 g/day: HRs 1.92 (1.10, 3.33) and 1.74	*No reliable evidence of an association* There was inconsistent evidence within alcohol consumption levels regarding whether higher amounts of alcohol per day were related significantly to anxiety or not.	Critical
				Drinking above guidelines vs within guidelines: HR=2.00 (1.31, 3.04), p<0.05	*Limited evidence of an association* A single study reported that women who drank above drinking guidelines level (0-168g /week) had significantly more likelihood of anxiety than those who drank below guidelines.	Critical
PTSD	N=0 K=0					

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Alcohol related psychoses	N=0 K=0				*No evidence for this outcome*	Important

Question: What is the effect of alcohol on mental health outcomes (across ages)?
Patient or population: Males, general population (across youth and adults)
Exposure: 5 drinks or over per week, or being monthly or weekly drinker, unhealthy alcohol use, >9 drinks/week
Reference group: less than 5 drinks per week, or never drinker

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=16,994 K=3 prospective cohort studies (Onwuameze et al. 2013; Ruggles et al. 2017; Sui et al. 2009)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	≥5 vs <5 drinks per week: OR=1.01 (0.87, 1.18) >9 vs <9 drinks per week: RR=0.94 (0.79, 1.13) Unhealthy alcohol use (≥4 on AUDIT-C): OR=1.09 (95%cI not stated)	*No reliable evidence of an association* Three studies provided consistent evidence that males drinking above particular thresholds (5 or 9 drinks per week, or AUDIT-C score 4) did not have a significantly increased likelihood of having depression compared to those drinking below the thresholds. Due to the risk of bias in the studies, the certainty of the evidence is low.	Critical
	N=6,220 K=2 prospective cohort studies (Meng 2017a; Meng et al. 2017b)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Monthly drinker vs < monthly drinker: HR=0.79 (0.64, 0.98) Monthly drinker vs never drinker: RR=0.45 (0.33, 0.62) Occasional drinker vs never drinker: RR=2.62 (1.93, 3.56)	*Limited evidence of an association* Two studies were consistent that men who drank more than once per month were less likely to have depression at follow-up, than those who abstained or drank less regularly. One of these studies also reported that those who drank occasionally had significantly more chance of depression at follow-up than those who abstained.	Critical
Suicidal ideation	N=73,710 K=1 cross-sectional study (Glasheen et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	HED vs no HED and suicidal ideation athe same time point: OR=1.63 (1.43, 1.85)	*Limited evidence of an association* A single cross sectional study reported that HED was significantly associated with suicidal ideation in unadjusted analyses.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Suicide attempts	N=73,710 K=1 cross-sectional study (Glasheen et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	HED vs no HED and suicide attempts athe same time point: OR=2.64 (1.76, 3.95)	*No reliable evidence of an association* A single cross sectional study reported that in males without MDE, there was no significant difference in the suicide attempts between HED and non-HED participants	Important
				Interaction between MDE and HED and suicide attempt adjusted Wald χ^2=0.01(1), p=0.989	*No reliable evidence of an association* There was no interaction between HED and MDE on the likelihood of suicide attempt in males.	Important
Anxiety	N=18,146 for males and females (N not stated by sex) K=1 prospective cohort study (Flensborg-Madsen et al. 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Drinking above guidelines vs within guidelines: HR=0.79 (0.42, 1.50)	*No reliable evidence of an association* A single study reported that men who drank above drinking guidelines level (0-252g /week) had no difference in later anxiety levels than those who drank within guideline levels.	Critical
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0				*No evidence for this outcome*	Important

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Adolescents (males and females combined)
Exposure: HED frequency, volume of alcohol consumed (quantity x frequency), weekly consumption, heavy/excessive or HED
Reference group: HED frequency, volume of alcohol consumed (quantity x frequency), <weekly consumption, abstinence or non-hazardous drinking

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=0 K=0				*No evidence for this outcome*	Critical
Depressive symptoms	N=4,841 K=2 prospective cohort studies (Hooshmand, Willoughby & Good 2012; Mason, WA et al. 2008)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Cross-sectional correlations of alcohol *quantity* consumed and depressive symptoms at the same time point: r=0.04 (p>0.05), to *r*=0.16 (p<0.05) ß=0.11, p<0.01	*Limited evidence of an association* Two studies reported on an association between volume of alcohol consumed and levels of depressive symptoms at the same time point. The two factors were significantly correlated at ages 14 to 16, but not at age 17.	Important
	N=4,841 K=2 prospective cohort studies (Hooshmand, Willoughby & Good 2012; Mason, WA et al. 2008)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Correlations of alcohol *quantity* consumed and depressive symptoms at later time point: r=0.07, p<0.05, to 0.14, p<0.05. ß=0.10, not significant.	*Limited evidence of an association* Two studies reported on an association between volume of alcohol consumed and levels of depressive symptoms a year or two later. The larger study reported all correlations were significant, while the smaller study showed an effect in the same direction, but was not statistically significant.	Important
	N=5,768 K=3 prospective cohort studies (Hooshmand, Willoughby &	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0	⨁⊖⊖⊖	Cross-sectional data of correlations of alcohol *frequency* consumed and depressive symptoms at same time point: r=0.11,	*Limited evidence of an association* Three studies reported significant cross-sectional correlations between alcohol frequency and depressive symptoms.Two studies reported significant correlations at all age (14 to 17 years), while the third study reported	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	Good 2012; Mason, WA et al. 2008; Scholes-Balog et al. 2015)	Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		p<0.05 to r=0.22, p<0.05 ß=0.049, p>0.05 to ß=0.19, p<0.05	significant correlations at 14 years but correlations which were not statistically significant at 11 or 16 years.	
	N=6,388 K=4 prospective cohort studies (Hooshmand, Willoughby & Good 2012; Mason, WA et al. 2008; Parrish et al. 2016; Scholes-Balog et al. 2015)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Correlations of alcohol *frequency* consumed and depressive symptoms at later time point: r=0.09 to 0.11 (all p<0.05) ß=-0.05 to 0.22, p<0.001	*Limited evidence of an association* Three out of four studies reporting on the association between frequency of alcohol consumption and depressive symptoms found significant positive correlations.	Important
	N=544 K=2 prospective cohort studies (Mackie, Castellanos-Ryan & Conrod 2011; Mason, W & Spoth 2011)	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Cross-sectional correlations of alcohol *frequency x quantity* and depressive symptoms at the same time point: r=0.14, p<0.05 to 0.20, p<0.001 β=0.24, p<0.05	*Limited evidence of an association* Two small studies reported that cross-sectional correlations between alcohol frequency x quantity and depressive symptoms were significant at ages 14, 15 and 16.	Important
	N=7,507 K=3 prospective cohort studies (Mackie, Castellanos-Ryan & Conrod 2011; Mason, W & Spoth 2011;	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0	⊕⊖⊖⊖	Correlations of alcohol *frequency x quantity* and depressive symptoms at later time point: r=0.08 to r=0.12, p>0.05 β=0.27, p<0.05 rho=0.072, p<0.001	*Limited evidence of an association* Two out of three studies reported an association between alcohol quantity x frequency and depressive symptoms. The remaining study had results in the same direction, but was too small for the results to be statistically significant.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	Patwardhan et al. 2017)	Confounding: 0				
	N=10,828 K=1 prospective cohort study (Needham 2007)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	HED frequency at age 15 and depressive symptoms at age 21: *B*=−0.20, p<0.001	*Limited evidence of an association* A single large study reported that high levels of HED at baseline was associated with higher levels of depressive symptoms at baseline, as well as being associated with a faster rate of decline in depressive symptoms over the next 6 years.	Important
	N=1,312 K=2 prospective cohort studies (Birkley, Zapolski & Smith 2015; McCarty et al. 2012)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Cross-sectional correlations of *Any* alcohol consumption and depressive symptoms at the same time point: phi=0.13 (p<0.05) to phi=0.21, (p<0.001) β=0.15 (p<0.01) to β=0.23 (p<0.01)	*Limited evidence of an association* Both studies reported positive associations between adolescents (aged 11 – 14 years) drinking any alcohol (more than a few sips) and depression at the same point.	Important.
	N=1,312 K=2 prospective cohort studies (Birkley, Zapolski & Smith 2015; McCarty et al. 2012)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*Any* alcohol consumption and depressive symptoms at later time point: phi=0.14, p<0.05 β=0.02 (p>0.05) to β=0.17, p<0.001	*Limited evidence of an association* Both studies reported positive associations between adolescents (aged 11 – 14 years) drinking any alcohol (more than a few sips) and depression at later time points. One study reported that correlations were not significant for depression at age 13, but the study was underpowered.	Important.

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=1,102 K=1 prospective cohort study (Skogen et al. 2016)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*Weekly* alcohol consumption by age 13: β=0.40 (0.16, 0.65), p<0.05 < weekly alcohol consumption by age 13: β=0.15 (−0.09, 0.39) Late onset (no drinking until age 18): β=0.14 (−0.12, 0.41)	*Limited evidence of an association* Children who were drinking weekly at age 13, were more likely to have depressive symptoms at ages 15 – 18. Only one time-point showed a significant association between occasional drinking and depressive symptoms. There was no association between regular drinking and having depressive symptoms, if the drinking was started after age 13.	Important
	N=6,113 K=4 prospective cohort studies (Chan, Kelly & Toumbourou 2013; Gustafson 2012; Mason, W & Spoth 2011; Mason, WA et al. 2008)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*HED or drinking to intoxification* and depressive symptoms at the same time point rho=0.13, p<0.05 to 0.20, p<0.001 β=0.11, p>0.05 (n=429) r=0.141, p<0.01 to 0.20, p<0.05	*Limited evidence of an association* Three out of four studies reported significant cross-sectional associations between HED or drinking to intoxification, and depressive symptoms. The remaining study was small so may have been underpowered.	Important
	N=9,726 K=6 prospective cohort studies (Chan, Kelly & Toumbourou 2013; Cisler et al. 2012; Gustafson 2012; Mason, W & Spoth 2011; Mason, WA et al. 2008; Skogen et	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*HED or drinking to intoxification* and depressive symptoms at 1-12 years later rho=0.08 (p<0.05) to 0.15, p<0.05 β=-0.065 (p<0.05) to 0.37, (p<0.05) r=0.029 (p>0.05) to 0.069 (p<0.05)	*No reliable evidence of an association* The majority of the studies showed a positive association between HED, and later depressive symptoms (up to 6 years). However, one study found negative associations, suggesting that HED may result in fewer depressive symptoms.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	al. 2016)					
	N=1,883 K=1 prospective cohort study (Pesola et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	*Heavy or harmful drinking* (not defined) and depressive symptoms at the same time point rho=0.13, p<0.05	*Limited evidence of an association* A single large study reported a cross-sectional association between heavy or harmful drinking and depressive symptoms at the same time point.	
	N=2,985 K=2 prospective cohort studies (Pesola et al. 2015; Skogen et al. 2016)	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*Heavy or harmful drinking* (not defined) and depressive symptoms at a later time point rho=0.33, p<0.001 β=0.35, p<0.05 to β=0.40, p<0.05	*Limited evidence of an association* Two studies reported significant associations between heavy or harmful drinking and depressive symptoms 2-5 years later.	Important
Suicidal ideation	N=15,363 K=1 cross-sectional study (Gart & Kelly 2015)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	HED and suicidal ideation at the same time point: *B*=0.02, β=0.02, p=0.027	*Limited evidence of an association* One large cross-sectional study at high risk of bias reported that HED and suicidal ideation were significantly associated. The direction of effect was not determined.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=6,540 K=1 cross-sectional study (Peltzer & Pengpid 2015)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 years vs non-initiators: OR=1.95 (1.32, 2.89) <12 years vs non-initiators: OR=3.39 (2.44, 4.71)	*Limited evidence of an association* One large cross-sectional study with a low risk of bias reported that those who had started drinking alcohol as a pre-teen or teen were more likely to have suicidal ideation than those who did not consume alcohol.	Important
	N=1,039 K=1 cross-sectional study (Souza et al. 2010)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Drank alcohol in past month vs abstinence: OR=1.64 (1.04, 2.58), p=0.033	*Limited evidence of an association* A single cross-sectional study reported that those who drank alcohol in the past month were more likely to also have suicidal ideation than those who were abstinent, to also have suicidal ideation. The direction of effect is unknown.	Important
				Drunkenness in past month vs no drunkenness: OR=1.94 (0.86, 4.36)	*No reliable evidence of an association* A single cross-sectional study reported that those who got drunk in the past month were more likely to also have suicidal ideation than those who did not, but after adjusted analysis this was not significant.	Important
Suicide attempt	N=47,316 K=2 cross-sectional studies (Gart & Kelly 2015; Schilling et al. 2009)	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	HED and suicide attempt at the same time point: *B*= 0.03, β=0.05, p<0.001 *B*=0.20 (0.06, 0.34), p<0.05 and	*Limited evidence of an association* Two large cross-sectional studies were consistent in reporting that there were significant associations between HED and attempting suicide in adolescents. In further analyses, one of these studies determined that the association between 'drinking while down' and suicide attempt was much stronger than for HED, and so the motive for drinking was more important than the occurrence of HED.	Important.
	N=6,540 K=1 cross-sectional study	Risk of bias: 0 Inconsistency: N/A Indirectness: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 years vs non-	*Limited evidence of an association* One large cross-sectional study with a low risk of bias reported that those who had started drinking alcohol as	Important.

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	(Peltzer & Pengpid 2015)	Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		initiators: OR=1.64 (1.16, 2.32) <12 years vs non-initiators: OR=4.55 (3.34, 6.21)	a pre-teen or teen were more likely to attempt suicde than those who did not consume alcohol. The direction of effect is unknown.	
Anxiety	N=2,070 K=1 prospective cohort study (Fröjd et al. 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	*Drinking at least once per week vs less than weekly:* OR=1.3 (0.6, 2.8)	No reliable evidence of an association A single study found no association between frequency of gettingweekly drinking and anxiety at a later time point.	Critical
				Drunk at least once a week vs less than weekly: *OR=0.8 (0.2, 3.6)*	*No reliable evidence of an association* A single study found no association between frequency of getting drunk and anxiety at a later time point.	Critical
Anxiety symptoms	N=620 K=1 prospective cohort study (Parrish et al. 2016)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	*Drinking frequency:* ß=0.02, p>0.05	*No reliable evidence of an association* A single study showed that drinking frequency in 14 year olds did not predict anxiety symptoms at 16 years.	Important
	N=780 K=2 prospective cohort studies (Mackie, Castellanos-Ryan & Conrod 2011; Pardee, Colder & Bowker 2014)	Risk of bias: -2 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0	⨁⨀⨀⨀	*Drinking quantity x frequency* There was no significant directional effects between Q×F and anxiety (p>0.39). B=0.001, p>0.05	*No reliable evidence of an association* Two studies were consistent in that quantity x frequency of alcohol consumed was not a significant predictor of anxiety symptoms after 6 months to 3 years.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Confounding: 0				
	N=3,614 K=1 prospective cohort study (Cisler et al. 2012)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	For PTSD 1 year later: Multiple imputations: ß=0.02, t=1.01, p>0.05 For PTSD 2 years later: Multiple imputations: ß=0.14, t=2.20, p<0.05	*Limited evidence of an association* HED frequency predicted PTSD diagnosis after 2 years, but not after 1. This study was not adjusted for multiple comparisons, and is therefore at risk of a type II error.	Important
PTSD	N=3,614 K=1 prospective cohort study (Cisler et al. 2012)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	For PTSD 1 year later: Multiple imputations: ß=0.02, t=1.01, p>0.05 For PTSD 2 years later: Multiple imputations: ß=0.14, t=2.20, p<0.05	*Limited evidence of an association* HED frequency predicted PTSD diagnosis after 2 years, but not after 1. This study was not adjusted for multiple comparisons, and is therefore at risk of a type II error.	Important
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Female adolescents
Exposure: Alcohol frequency, HED, moderate drinking
Reference group: Never HED, low drinking

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=6,466 K=1 prospective cohort study (Powers, J et al. 2016)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	*HED:* Rarely vs never: OR=1.02 (0.82, 1.27) Monthly vs never: OR=0.94 (0.75, 1.17) Weekly vs never: OR=0.93 (0.76, 1.14) >Weekly vs never: OR=1.30 (1.04, 1.63)	*Limited evidence of an association* One large study reported that HED more frequently than once per week when aged 16-21 was significantly associated with having depression between ages 22 and 27. HED weekly or less was not associated with depression.	Critical
	N=2,414 K=1 prospective cohort study (Edwards et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Moderate vs low drinking: OR=1.63 (1.04, 2.55), p<0.05 High vs low drinking: OR=1.93 (1.08, 3.44), p<0.05	*Limited evidence of an association* One study reported that 14 year old girls who drank moderately or highly (occasionally or weekly) were significantly more likely to have depression at age 16 than those who didn't drink.	Critical
Depressive symptoms	N=661 K=2 prospective cohort studies (Fleming et al. 2008; Wymbs et al. 2014)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0	⨁⨀⨀⨀	*Alcohol frequency* Correlation coefficients: ß=0.10 to 0.23 (not significant)	*No reliable evidence of an association.* No significant association was found between frequency of alcohol consumption and depressive symptoms, although a consistent trend was identified, and the studies were small.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Confounding: 0				
	N=291 K=1 prospective cohort study (Danzo, Connell & Stormshak 2017)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	*Quantity x frequency* and depressive symptoms at the same time point Correlation coefficients: r=0.29 (p<0.05) to 0.38 (p<0.05)	*Limited evidence of an association* A single small study reported that cross-sectional associations between quantity x frequency of alcohol and concurrent depressive symptoms were significant at all ages for female adolescents (12 to 15 years).	Important
	N=291 K=1 prospective cohort study (Danzo, Connell & Stormshak 2017)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	*Quantity x frequency* and depressive symptoms at a 1-3 years later Correlation coefficients: r=0.07 (p>0.05) to 0.30 (p<0.05)	*Limited evidence of an association* A single small study reported on the association of quantity x frequency and depressive symptoms after 1 to 3 years. The correlations were significant at nearly all time points, suggesting that in females, the number of drinks consumed in a month over ages 12 – 14 predict depressive symptoms 1 to 3 years later.	Important
	N=15,167 K=3 prospective cohort studies (Needham 2007; Pesola et al. 2015; Wilkinson, Halpern & Herring 2016)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*HED* Correlation coefficients: β=−0.03 (−0.09, 0.03) β=0.01 (SE 0.01) *B*=-0.03, p<0.001	*No reliable evidence of an association* One study reported that HED was associated with a faster reduction in depressive symptoms, while the remaining two studies reported no association.	Important
	N=3,096 K=1 prospective	Risk of bias: 0 Inconsistency: N/A	⨁⨁⨁⊖	*HED* Time-varying coefficients	*Evidence of an association* A single high quality study reported significant	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	cohort study (Schuler, Vasilenko & Lanza 2015)	Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		β~0.4 (0.0, 0.8) to 3.7 (2.1m 5.3)	associations between HED and depressive symptoms during adolescence (with predictors and outcomes as continuous functions of time, i.e. both predictors and outcomes measured at the same multiple time points).	
Suicidal ideation	N=35,001 K=2 cross-sectional studies (Kim & Kim 2010; Peltzer & Pengpid 2015)	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 or 13 years vs non-initiators: ORs=1.21 (1.12, 1.30) and 2.12 (1.34, 3.34) <12 or 13 years vs non-initiators: ORs=1.34 (1.33, 1.59) and (3.12 (1.95, 4.90)	*Limited evidence of an association* Two cross-sectional studies reported consistent evidence that girls who start consuming alcohol before age 12 or 13 have a higher risk of having suicidal ideation than those who do not start drinking alcohol. Those who start drinking as a teen also have a higher risk than those who don't start drinking.	Important
Suicide attempts	N=35,001 K=2 cross-sectional studies (Kim & Kim 2010; Peltzer & Pengpid 2015)	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 or 13 years vs non-initiators: ORs=1.23 (1.05, 1.43) and 2.31 (1.51, 3.52) <12 or 13 years vs non-initiators: ORs=1.61 (1.37, 1.89) and 5.76 (3.84, 8.64)	*Limited evidence of an association* Two cross-sectional studies reported consistent evidence that girls who start consuming alcohol before age 12 or 13 or as a teen have a higher risk of attempting suicide than those who don't start drinking as an adolecent.	Important
Anxiety	N=2,414 K=1 prospective cohort study (Edwards et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0	⊕⊕⊖⊖	Moderate vs low drinking: OR=1.25 (0.88, 1.77) High vs low drinking: OR=1.78 (1.13, 2.81), p<0.05	*No reliable evidence of an association.* One study reported that teenage girls who drank weekly were more likely to have anxiety after 2 years than those who did not drink. However, after adjustments for housing tenure and conduct problems, this was no	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0			longer significant.	
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Male adolescents
Exposure: Alcohol frequency, moderate or high consumption, quantity, frequency, quantity x frequency, HED
Reference group: Low alcohol consumption, non-HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=1,878 K=1 prospective cohort study (Edwards et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Moderate vs low alcohol consumption: 2.25 (1.09, 4.66), p<0.05 High vs low alcohol consumption: 2.54 (1.06, 6.10), p<0.05	*Limited evidence of an association* One study showed that moderate alcohol consumption (occasional use) and high levels of consumption (weekly use) in 14 year old males, significantly predicted having a depressive episode by age 16.	Critical
Depressive symptoms	N=745 K=2 prospective cohort studies (Fleming et al.	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1	⨁⊖⊖⊖	*Alcohol frequency* and depressive symptoms at the same time point Correlation coefficients:	*No reliable evidence of an association* Two small studies reported cross-sectional associations between frequency of alcohol consumption and level of depressive symptoms. One study reported no significant association at any age (13-16 years), while the second	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	2008; Wymbs et al. 2014)	Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		ß=0.05 (p>0.05) to ß=0.16 (p<0.05)	study reported no association at age 14, but a significant association at age 15.	
	N=745 K=2 prospective cohort studies (Fleming et al. 2008; Wymbs et al. 2014)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	*Alcohol frequency* and depressive symptoms at later time points Correlation coefficients: ß=0.02 to 0.13	*No reliable evidence of an association* Two small studies reported no significant association was found between frequency of alcohol consumption and depressive symptoms.	Important
	N=302 K=1 prospective cohort study (Danzo, Connell & Stormshak 2017)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	*Quantity x frequency* and depressive symptoms at the same time point Correlation coefficients: r=0.09 (p>0.05) to 0.28 (p<0.05)	*No reliable evidence of an association* A single small study reported on the association of quantity x frequency and concurrent levels of depressive symptoms in adolescent males. The association was significant at age 14, but not at ages 12, 13 or 15.	Important
	N=302 K=1 prospective cohort study (Danzo, Connell & Stormshak 2017)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	*Quantity x frequency* and depressive symptoms at 1 to 3 years later Correlation coefficients: r=0.00 (p>0.05) to 0.17 (p<0.05)	*No reliable evidence of an association* A single small study reported on the association of quantity x frequency and depressive symptoms after 1 and 2 years. Only 1/6 correlations was significant, suggesting that overall, the number of drinks consumed in the past month does not predict depressive symptoms.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=12,519 K=3 prospective cohort studies (Needham 2007; Pesola et al. 2015; Wilkinson, Halpern & Herring 2016)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	*HED* Correlation coefficients: β=−0.03 (−0.10, 0.05) β=−0.01 (SE 0.01) and *B*=−0.06 (0.03), p<0.05	*No reliable evidence of an association* Three studies were consistent that there was no significant association between between HED in male adolescents, and levels of depressive symptoms 2-13 years later.	Important
	N=2974 K=1 prospective cohort study (Schuler, Vasilenko & Lanza 2015)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	*HED* Age-related coefficients: β=0.0 (-0.3, 0.3) to 2.1 (1.7, 4.4)	*Evidence of an association* A single large good quality study reported significant associations between HED and depressive symptoms at ages 12 and 17 years, but non-significant associations at ages 18.5 and 31 years. The associations were smaller in males than female adolescents.	Important
Suicidal ideation	N=35,263 K=2 cross-sectional studies (Kim & Kim 2010; Peltzer & Pengpid 2015)	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 or 13 years vs non-initiators: ORs= OR=1.11 (1.01, 1.22) and 1.88 (1.14, 3.10) <12 or 13 years vs non-initiators: ORs=1.28 (1.16, 1.41), and 3.37 (2.16, 5.27)	*Limited evidence of an association* Two cross-sectional studies reported consistent evidence that boys who start consuming alcohol before age 12 or 13 have a higher risk of having suicidal ideation than those who do not start drinking alcohol. Those who start drinking as a teen also have a higher risk than those who don't start drinking.	Important
Suicide attempts	N=35,263 K=2 cross-sectional	Risk of bias: 0 Inconsistency: 0	⊕⊕⊖⊖	Age at alcohol consumption initiation: ≥12 or 13 years vs non-	*No reliable evidence of an association* Two cross-sectional studies reported consistent evidence that boys who start consuming alcohol as a	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	studies (Kim & Kim 2010; Peltzer & Pengpid 2015)	Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		initiators: ORs=1.06 (0.89, 1.27), n=13,595 and 1.19 (0.77, 1.85)	teen are not at an increased risk of suicide attempt compared to those who have not started drinking.	
				Age at alcohol consumption initiation: <12 or 13 years vs non-initiators: ORs=1.27 (1.06, 1.52) and 3.94 (2.46, 6.32)	*Limited evidence of an association* Two cross-sectional studies reported consistent evidence that boys who start consuming alcohol before age 12 or 13 have a higher risk of attempting suicide than those who don't start drinking as an adolecent.	
Anxiety	N=1,878 K=1 prospective cohort study (Edwards et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Moderate vs low drinking: OR=1.13 (0.65, 1.95) High vs low drinking: OR=1.20 (0.55, 2.62)	*The evidence shows no association* No association was found between occasional or weekly drinking and anxiety after 2 years.	Critical
Anxiety symptoms	N=503 K=1 prospective cohort study (Cerdá et al. 2016)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Alcohol frequency: ß=−0.00002 (95%CI −0.003, 0.003) Alcohol quantity: age 13-14: ß=−0.36 (95%CI −0.62, −0.11), p<0.05 age 15-16: ß=−0.26 (95%CI −0.84, 0.32) age 17-19: ß=−0.20 (95%CI −0.38, −0.02), p<0.05	*Limited evidence of an association* A single study reported significant associations between the volume of alcohol consumed per drinking occasion and the level of anxiety symptoms reported 13 years later.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Young adults (males and females combined)
Exposure: Any alcohol consumption, medium-risk drinking, high-risk drinking, HED/heavy drinking, alcohol quantity, frequent HED
Reference group: No alcohol consumption, low-risk drinking, occasional HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depressive symptoms	N=429 K=1 prospective cohort study (Mason, WA et al. 2008)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Cross-sectional correlation between consumption *quantity* and depressed mood at age 18: β=0.10 Cross-sectional correlation between consumption *frequency* and depressed mood at age 18: β=0.07	*No reliable evidence of an association* The single small study in young adults assessing link between alcohol consumption quantity or frequency and concurrent diagnosis diagnosis of depression reported no significant association between either quantity or frequency of alcohol consumption a.	Critical
Depressive symptoms	N=429 K=1 prospective cohort study (Mason, WA et al. 2008)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Alcohol consumption *quantity:* β=0.06 Alcohol consumption frequency: β=0.03	*No reliable evidence of an association* A single study reported that there was no significant association between quantity of alcohol at age 18 and depressed mood at age 22 as a continuous variable. Likewise, there was no association between frequency of alcohol consumption at age 18 and depressed mood at age 22 as a continuous variable.	Important
	N=522 K=1 prospective cohort study (Armeli, Sullivan &	Risk of bias: 0 Inconsistency: N/A Indirectness: 0	⨁⨁⨀⨀	Alcohol *quantity x frequency*: *b*=0.001	*No reliable evidence of an association* One small study found no association between total alcohol consumed (quantity x frequency) and depressive symptoms.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	Tennen 2015)	Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0				
	N=4,809 K=3 prospective cohort studies (Gustafson 2012; Mason, WA et al. 2008; Piasecki, Trela & Mermelstein 2017)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	*Frequency of HED* and depressive symptoms at the same time point Correlations: r=-0.004 to 0.01 β=-0.009 to 0.05	*No reliable evidence of an association* Three studies were consistent that there was no significant cross-sectional association between HED and depressive symptoms in young adults.	Important
	N=4,809 K=3 prospective cohort studies (Gustafson 2012; Mason, WA et al. 2008; Piasecki, Trela & Mermelstein 2017)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	*Frequency of HED* Correlations: r= -0.045 ($p<0.05$) to r=0.01 ($p>0.05$) β=-0.026 to 0.05	*No reliable evidence of an association* One out of three studies reported a statistically significant negative association between HED and a reduced number of depressive symptoms.	Important
	N=7,386 K=1 prospective cohort study (Sloan, Grossman & Platt 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0	⊕⊕⊖⊖	Frequent HED vs occasional HED Difference in propensity scores: 3.7 (95%CI 0.41, 7.1)	*Limited evidence of an association* A single study reported that frequent HED drinkers had higher depressive symptoms than occasional HED drinkers.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Confounding: 0				
Suicide attempts	N=0 K=0					
Anxiety	N=0 K=0					Critical
PTSD	N=904 K=1 prospective cohort study (Read et al. 2016)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: -2 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	ORs for transitioning to PTSD or more severe PTSD with alcohol vs no alcohol: 0.76 – 1.35 ORs for transitioning to no PTSD or less severe PTSD with alcohol vs no alcohol: 0.82 – 1.34	*No reliable evidence of an association* There was a similar likelihood of that any alcohol consumption was associated with PTSD or worsening of PTSD as there was of alcohol consumption being associated with no longer having PTSD or improving PTSD	Important
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Young adults (females)
Exposure: Any alcohol consumption, medium-risk drinking, high-risk drinking, HED/heavy drinking, alcohol quantity, frequent HED
Reference group: No alcohol consumption, low-risk drinking, occasional HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=1,196 K=1 prospective cohort study (Zhang et al. 2018)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1	⨁⨁⨀⨀	*Alcohol quantity* and depression 17 months later: Medium risk (20-40	*No reliable evidence of an association* A single large study reported that the average quantity which young adult women drank per day did not predict the likelihood of developing depression 17 months later.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		g/day) vs low risk (<20 g/day): OR=1.50 (0.56, 4.05) High risk (>40 g/day) vs low risk (<20 g/day): OR=1.73 (0.37, 8.18)	However, the large confidence intervals suggest that this study may have been underpowered for this outcome.	
Depressive symptoms	N=249 K=1 prospective cohort study (Wymbs et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	*Drinking frequency* and depressive symptoms at the same time: β=0.18	*No reliable evidence of an association* A single small study reported no significant association between drinking frequency and cross-sectional levels of depressive symptoms in young adult women. However, this study may have been underpowered.	Important
	N=200 K=1 prospective cohort study (Mushquash et al. 2013)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	*HED* and depressive symptoms at 1-2 weeks later: β=0.02 to 0.05	*No reliable evidence of an association* A single small study found no significant association between HED and depressives symptoms a short time later.	Important
Suicide attempts	N=0 K=0					
Anxiety	N=0 K=0					Critical
PTSD	N=0 K=0					

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol on mental health outcomes in youth?
Patient or population: Young adults (males)
Exposure: Any alcohol consumption, medium-risk drinking, high-risk drinking, HED/heavy drinking, alcohol quantity, frequent HED
Reference group: No alcohol consumption, low-risk drinking, occasional HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depressive symptoms	N=272 K=1 prospective cohort study (Wymbs et al. 2014)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Alcohol *frequency* at the same time point β=−0.17, p>0.05	*No reliable evidence of an association* A single small study reported no association between frequency of alcohol consumption in young adult males, and depressive symptoms at the same time point.	Important
	N=4,617 K=1 prospective cohort study (Grazioli et al. 2018)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Alcohol *quantity x frequency (total drinks per week)* and depressive symptoms at the same time*:* rho=0.06 and 0.08 (both p<0.001)	*Limited evidence of an association* A single large study in males, reported that alcohol quantity x frequency (total drinks consumed per week) was significantly positively correlated with depressive symptoms at the same time point (unadjusted). The direction of effect is unknown.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=4,617 K=1 prospective cohort study (Grazioli et al. 2018)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Alcohol *quantity x frequency (total drinks per week)* and depressive symptoms 15 months later: rho=0.03, p<0.05 β=−0.100 [−0.145, −0.053]	*Limited evidence of an association* A single large study in males, reported that amount of alcohol consumed per week was associated with fewer depressive symptoms after adjusting for covariates such as drinking to cope (i.e. positive effect is for drinking for pleasure, rather than drinking in total).	Important
	N=4,617 K=1 prospective cohort study (Grazioli et al. 2018)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	*HED* and depressive symptoms at the same time*:* rho=0.04 to 0.07 (both p<0.05)	*Limited evidence of an association* A single large study in males, reported that HED was associated with the concurrent level of depressive symptoms (unadjusted).	Important
	N=4,617 K=1 prospective cohort study (Grazioli et al. 2018)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	*HED* and depressive symptoms 15 months later: rho=0.03, p>0.05 β=−0.144 (-0.224, -0.065)	*No reliable evidence of an association.* A single large study in males, reported that frequency of HED was not correlated with depressive symptoms 15 months later in unadjusted analyses. Significant associations were found after adjusted for drinking to cope.	Important
Suicide attempts	N=4,617 K=1 prospective cohort study (Grazioli et al. 2018)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0	⨁⨁⨀⨀	Direct effect: alcohol on suicide Total drinks /week: β=−0.019 (−0.289, 0.260) HED: β=0.119 (−0.408,	*No reliable evidence of an association* Alcohol use (total drinks per week or HED) was not directly associated with suicide attempts. Indirect effects were found through the effect of alcohol on baseline depressive symptoms.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		0.665)		
Anxiety	N=0 K=0					Critical
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					
Evidence statements: *No reliable evidence of an association between alcohol consumption and mental health outcomes was identified in young adults (GRADE ⊕⊖⊖⊖ to ⊕⊕⊕⊖).* *Limited evidence suggests that frequent HED in young adults may be associated with a higher risk of depressive symptoms than occasional HED (k=1; GRADE ⊕⊕⊖⊖).*						

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Adults general population
Exposure: Weekly alcohol consumption, alcohol in toxicology, low consumption, hazardous or harmful consumption, HED
Reference group: Not stated (assumed abstinence or consumption less than weekly), abstainers

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=7,478 K=1 prospective cohort study (Bell & Britton 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 1 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Abstainers vs drinking within guidelines (≤21g for men; ≤14g for women per week): HR=1.02 (0.89, 1.16) Exceeding guidelines vs within guidelines: HR=0.86 (0.53, 1.39)	*No reliable evidence of an association* A single study reported no difference in rate of depression over a 28 year period in those who drank within guidelines and either abstainers or those who exceed drinking guidelines.	Critical
	N=7,478 K=1 prospective cohort study (Bell & Britton 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 1 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	HED vs non-HED drinkers: HR=1.0 (0.91, 1.15) Abstinent vs non-HED drinkers: HR=1.23 (0.98, 1.53)	*No reliable evidence of an association* A single study reported no difference in rate of depression over a 28 year period between those who drank without HED, vs either abstinence or HED	Critical
	N=7,478 K=1 prospective cohort study (Bell & Britton	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 1	⊕⊕⊖⊖	Hazardous drinkers (>40g/session) vs non-hazardous drinkers: HR=0.81 (0.49, 0.86)	*Limited evidence of an association* A single study reported a statistically significant difference in the rate of depression over 28 years, such that those who participated in hazardous drinking at baseline had a lower rate of depression than non-hazardous drinkers.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	2015)	Large effect: 0 Confounding: 0				
	N=7,478 K=1 prospective cohort study (Bell & Britton 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 1 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Abstainers and daily drinkers vs weekly drinkers HR=1.24 (0.99,1.56) and 1.17 (1.05,1.32), p=0.01 Monthly and occasional drinkers vs weekly drinkers HR=1.07 (0.92,1.25) and 0.97 (0.83,1.15)	*Limited evidence of an association* One study reported that daily drinkers had a higher risk of depression over a 28 year period than weekly drinkers. there was a trend for abstainers having a higher risk of depression than weekly drinkers There was no difference in the odds of depression between weekly, monthly and occasional drinkers.	Critical
	N=13,619 K=1 prospective cohort study (Gea et al. 2012)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Low consumption vs abstainers: HRs=0.65 (0.49, 0.86) to 0.94 (0.75, 1.19)	*Limited evidence of an association.* A single large study reported that those who drank low levels of alcohol (<30g/day) had lower depression rates than those who were abstinent.	Critical
	N=13,619 K=1 prospective cohort study (Gea et al. 2012)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Hazardous or harmful consumption vs abstainers: HR=0.73 (0.50, 1.06)	*No reliable evidence of an association* One study provided evidence that moderate to high levels of alcohol (>15g/day) was not significant associated with the odds of depression.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depressive symptoms	N=15,926 K=1 prospective cohort study (Paljärvi et al. 2009)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 1 but not rated up due to risk of bias in the study Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Low consumption vs abstainers: ORs=1.02 (0.89, 1.04) to 1.16 (1,04, 1.30) Hazardous or harmful consumption vs abstainers: ORs=1.43 (1.28, 1.60)	*Limited evidence of an association* One study reported that anything over 10 g of alcohol per day for women, or over 15 g for men, was associated with an increased risk of depressive symptoms.	Important
Incident bipolar disorder	N=34,653 K=1 prospective cohort study (Cougle et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Weekly alcohol vs abstinence or <weekly alcohol: OR=0.79 (0.73, 0.86), p<0.001	*Limited evidence of an association* One study (with no adjustments for multiple comparisons) found that weekly alcohol use was associated with a reduced risk of being diagnosed with an incident bipolar disorder.	Important
Suicide	N=346 K=1 case control study (Conner et al. 2017)	Risk of bias: -1 Inconsistency: N/A Indirectness: -1 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	OR of dying by suicide rather than motor vehicle accident if blood toxicology showed alcohol alone or in combination with other drug: Alcohol alone vs neither: OR=1.22 (0.74, 2.00) Alcohol plus drug vs neither: OR=4.33 (1.70, 11.03), p<0.05	*No evidence of an association* There was no significant difference in the proportion of people dying by suicide or motor vehicle, based on whether they had alcohol in their blood stream or not. People who had alcohol and drugs in their blood stream, were more likely to die by suicide than motor vehicle accident than if they had neither in their blood.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
				Drug alone vs neither: OR=1.03 (0.37, 2.88)		
Suicidality (ideation or attempt)	N=3,813 K=1 cross-sectional study (Herberman Mash et al. 2016)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Quantity of alcohol per day: <48 g for men and 24.3 g for women per day, vs drinking more than these amounts: OR=1.04 (0.67, 1.65)	*No reliable evidence of an association* A single cross-sectional study reported that amount of alcohol consumed per day (light to moderate vs heavy) was not associated with suicidality rate, after adjustments for confounding factors such as motives for drinking.	Important
Anxiety	N=34,653 K=1 prospective cohort study (Cougle et al. 2015)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Weekly consumption vs less than weekly consumption: OR=0.88 (0.82, 0.95), p<0.01	*Evidence of an association* A large study from U.S. found that adults who consume alcohol at least weekly, have less chance of developing depression after 3 years, than those who drink less than weekly or abstain.	Critical
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Adult females

Exposure: Drinks per day, AUDIT score percentile, frequency of drinking
Reference group: Abstinence

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=7082 K=1 prospective cohort study (Gea et al. 2012)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Low consumption vs abstainer: HR=0.62 (0.42, 0.88) to 0.97 (0.75, 1.27) ORs=0.4 (0.1, 1.1) to 0.6 (0.4, 1.2) High consumption vs abstainer: HR=1.06 (0.43, 2.63) OR=3.3 (0.7, 14.8)	*No reliable evidence of an association* There was a (predominantly non-significant) trend supporting low levels of consumption (either in drinks/day or on AUDIT score percentile) compared with total abstinence. There was no significant difference in the odds of having depression at follow-up in abstainers or high consumers of alcohol.	Critical
	N=3,353 K=1 prospective cohort study (Augestad, Slettemoen & Flanders 2008)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Low frequency (no recent or 1-4 times in 2 weeks) drinking vs abstainer: OR=1.17 (0.61, 2.24) to 1.18 (0.61, 2.27) High frequency (≥10 times/2 weeks) vs abstainer: OR=0.72 (0.15, 3.47)	*No reliable evidence of an association* Neither low frequency drinking nor high frequency drinking was associated with depression 4-years later.	Critical
Depressive symptoms	N=306 K=1 prospective cohort study (Otten, van der Zwaluw & Engels 2018)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Mean no. of drinks consumed: β=0.05, p=0.36	*No reliable evidence of an association* A single study found no association between number of drinks consumed and level of depressive symptoms 4 years later.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Suicide	N=0 K=0					Important
Anxiety	N=approx. 9455 K=2 prospective cohort studies (Flensborg-Madsen et al. 2011; Johnson et al. 2013)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	>14 drinks/week vs <14 drinks/week: HR=2.00 (1.31, 3.04) >14 drinks/week vs abstainer: HR=1.92 (1.10, 3.33) No significant relationship between hazardous drinking (wave 1) and anxiety (wave 2).	*No reliable evidence of an association* One out of two studies reported a significant association between alcohol consumption and a higher risk of developing anxiety. The other small study reported no association.	Critical
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					Important

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Adult males
Exposure: Drinks per day, AUDIT score percentile, frequency of drinking
Reference group: Abstinence

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=6,537 K=1 prospective cohort study	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0	⨁⨁⊖⊖	Low consumption vs abstainer: HR=0.64 (0.39, 1.07) to 0.82 (0.50, 1.36) High consumption vs	*No reliable evidence of an association* No significant associations were found between alcohol consumption levels and the risk of depression at follow-up.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	(Gea et al. 2012)	Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		abstainer: HR=0.76 (0.40, 1.47)		
	N=3,308 K=1 prospective cohort study (Augestad, Slettemoen & Flanders 2008)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨀⨀	Low frequency (no recent or 1-4 times in 2 weeks) drinking vs abstainer: OR=0.62 (0.32, 1.21) to 0.75 (0.38, 1.49) High frequency (≥10 times/2 weeks) vs abstainer: OR=0.47 (0.16, 1.38)	*No reliable evidence of an association* Neither low frequency drinking nor high frequency drinking was associated with depression 4-years later.	Critical
Depressive symptoms	N=288 K=1 prospective cohort study (Otten, van der Zwaluw & Engels 2018)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Mean no. of drinks consumed: β=0.01, p=0.87	A single study found no association between number of drinks consumed and level of depressive symptoms 4 years later.	Important
Suicide	N=0 K=0					Important
Anxiety	N=approx. 9,073 K=1 prospective cohort study (Chou, Liang &	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0	⨁⨁⨀⨀	>21 drinks/week vs <21 drinks/week: HR=0.79 (0.42, 1.50)	*No reliable evidence of an association* A single study reported no significant difference in rate of anxiety based on alcohol quantity consumed per day (above or below 252 g/week).	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	Mackenzie 2011)	Large effect: 0 Confounding: 0				
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Older adult subgroup
Exposure: Weekly alcohol consumption / abstinent / occasional HED (<1 per month) / frequent HED (≥1 per month)
Reference group: Not stated (assumed abstinence or consumption less than weekly) / non-HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=8017 K=2 prospective cohort studies (Gea et al. 2013a; Weyerer et al. 2013)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Drinking ≤15g /day vs abstaining: HRs=0.72 (0.53, 0.98), p<0.05 to 0.97 (0.75, 1.25)	*No reliable evidence of an association* One out of two studies reported that elderly people who drank 5-15g of alcohol per day were less likely to have depression than those who abstained.	Critical
				Drinking >15 g/day vs abstaining: HRs=0.79 (0.53, 1.16) to 1.18 (0.79, 1.76)	*No reliable evidence of an association* Two studies were consistent that there was no significant difference in the rate of depression between those elderly people who were abstinent versus those who drank ≥20 g/day.	Critical
	N=25,619 K=2 prospective cohort studies (An & Xiang 2015; Luppa et al. 2012)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Heavy or at-risk drinking (≥14g/day for women and ≥30g/day for men) vs abstinence or non-heavy drinking: HRs=1.05 (0.98, 1.13) and 2.33 (1.09, 4.96)	*No reliable evidence of an association* Two studies compared heavy or at-risk drinking in an elderly population, against those who did not drink heavily. There was contradictory information, with one study reporting no difference in the rate of depression at follow-up, whereas the second study reported over a doubling of risk of subsequent depression in the high-alcohol consumption group. The reason for the heterogeneity is unclear.	Critical
Depressive symptoms	N=7,939 K=1 prospective cohort study (Brennan et al. 2016)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0	⨁⊖⊖⊖	Never drinkers: OR for increasing depressive symptoms=1.30, p>0.05. OR for decreasing depressive symptoms=1.13 Light drinkers: OR for	*No reliable evidence of an association* Different drinking levels had little influence on the whether participants had an increase or a decrease in their levels of depressive symptoms. Those with a drinking history (who were abstinent; data not shown here) had significantly higher chances of increasing depressive symptoms, as well as decreasing	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Large effect: 0 Confounding: 0		increasing depressive symptoms=0.76, p>0.05 OR for increasing depressive symptoms=0.66, p>0.05 Moderate drinkers: OR for increasing depressive symptoms=0.59, p<0.01 OR for decreasing depressive symptoms=0.62, p>0.05 Heavy drinkers: OR for increasing depressive symptoms=0.95, p>0.05 OR for decreasing depressive symptoms=1.50, p>0.05	depressive symptoms vs having consistently low depressive symptoms.	
	N=15,628 K=1 prospective cohort study (Cheng et al. 2016)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Drinking at least monthly vs being abstinent: OR=0.6 (0.5, 0.7) Drinking daily vs <daily: OR=1.2 (0.8, 1.7)	*Limited evidence of an association* A single study reported that those who drank at least monthly had reduced odds of having depression at follow-up, compared to those who never drank. No significant difference was found between those who drank daily or less than daily.	Important.
	N=3,273 K=1 prospective cohort study (Tsai, Chi & Wang 2013)	Risk of bias: 0 Inconsistency:N/A Indirectness: 0 Imprecision: 0 Publication bias: 0	⊕⊕⊕⊖	Moderate weekly drinker (<2 drinks/time) vs drinking less than weekly: OR=0.89 (0.63, 1.26) Heavy weekly drinker (≥2	*The evidence shows no association* A single good quality study reported no significant difference in likelihood of developing depressive symptoms, between those drink at least weekly, and at least 2 drinks per occasion, versus those who drink less than that.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Dose-response: 0 Large effect: 0 Confounding: 0		drinks/time) vs drinking less than weekly: OR=0.70 (0.30, 1.64)		
	N=10,463 K=2 prospective cohort studies (Lang et al. 2007; Paulson et al. 2018)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	1-2 drinks/day vs 0-1 drinks/day: z=−0.08 (−0.15, −0.02), p<0.05 ≤2 drink/day vs abstinent: β(SE)=0.151 (0.061), p=0.013	*Limited evidence of an association* Two studies reported that those who drank up to 2 drinks per day had lower rates of depressive symptoms at follow-up than those who didn't drink, or drank up to 1 drink per day.	Important
Anxiety	N=0 K=0					
PTSD	N=0 K=0					
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Older female subgroup
Exposure: Light, moderate, heavy drinking, short term risk drinking, long term risk drinking, HED, monthly drinking
Reference group: Abstinence, light drinking, non-HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=65,598 K=5 prospective cohort studies 1490165122092198(Chang et al. 2016; Gea et al. 2013b; Hiles et al. 2015; Tait et al. 2012; Tanaka et al. 2011)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Light-moderate drinkers vs being abstinent: HRs=0.83 (0.58, 1.18) to 0.99 (0.74, 1.18) ORs=0.67 (0.37,1.19) to 0.70 (0.33, 1.49) Abstinent vs light drinkers: OR=1.23 (1.14, 1.32) and z=0.31 (0.08, 0.54), p<0.01	*No reliable evidence of an association* Four studies were consistent that a light to moderate amount of alcohol per day (<40 g/day) was not significantly associated with either a risk reduction or increase in the risk of depression compared to abstinence. A single very large Australian study reported that those who were abstinent had significantly higher levels of depression at follow-up than those who consumed 0-20 g/day.	Critical
	N=27,314 K=3 prospective cohort studies 1490;2209(Chang et al. 2016; Hiles et al. 2015; Tanaka et al. 2011)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Heavy, or hazardous drinker (20 g/day) vs abstainer: HRs=1.13 (1.01, 1.26) ORs=0.36 (0.04, 3.43) to 0.39 (0.05, 3.08)	*No reliable evidence of an association* Few elderly people consumed hazardous amounts of alcohol, so two out of three studies were underpowered and had no significant association between heavy drinking (>20 or 40 g/day) and depression. The remaining study was very large and reported that heavy drinkers (>40 g/day) had an elevated risk of developing depression compared to abstainers.	Critical
	N=12,132 K=1 prospective cohort study (An & Xiang 2015)740	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Heavy vs non-heavy drinking or abstinence: HR=1.09 (0.98, 1.20)	*No reliable evidence of an association* When high consumption was compared against low consumption, there were no significant differences in the chance of having depression at follow-up.	Important
	N=31,202 K=1 prospective cohort study	Risk of bias: -2 Inconsistency: N/A Indirectness: 0	⨁⊖⊖⊖	Short term risk drinking (≥4 drinks/day) vs 0-2 drinks/day: OR=1.54 (1.22, 1.95),	*Limited evidence of association* A single study reported that short-term risk drinkers (4 drinks/day) had a higher likelihood of depression than low risk drinkers (0-2 drinks/day). Long-term risk	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	(Tait et al. 2012)	Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0		p<0.001 Long-term risk drinking vs 0-2 drinks/day: OR=1.22 (1.08, 1.38), p<0.05	drinkers (2-4 drinks/day) also had a higher likelihood of depression.	
	N=7,891 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011) #262	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨁⊖	HED frequency vs non-HED drinkers: OR=0.79 (0.56, 2.86) for HED ≥1 per month and OR=0.89 (0.52, 1.51) for <1 per month	*The evidence shows no association* A single study reported no significant difference in the likelihood of depression in people who participate in HED (< or ≥monthly) vs those who drink without HED.	Critical
Depressive symptoms	N=7,240 K=1 prospective cohort study (Byers et al. 2012) #2202	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨁⊖	Frequent vs non-frequent drinking or abstinence: OR=0.99 (0.69, 1.43)	*The evidence shows no association* When frequent drinking (≥14g alcohol /day) was compared against infrequent drinking, there were no significant differences in the chance of having depressive symptoms at follow-up.	Important
	N=8,175 K=1 prospective cohort study (Cheng et al. 2016) #753	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0	⨁⊖⊖⊖	Drinking more than once a month vs never drinking: OR=0.8 (0.5, 1.3) Drinking more than once a month vs former drinkers:	*No reliable evidence of an association* A single study at risk of bias reported no significant association between drinking at least monthly, and risk of depressive symptoms, compared to those who do not drink.	Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Confounding: 0		OR=1.3 (0.5, 3.8)		
	N=3,877 K=1 prospective cohort study (Lang et al. 2007) #638	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	≥1 drink/day (≥14 g alcohol) vs ≤1 drink/day: z=−0.02 (−0.13, 0.09) to z=0.00 (−0.21, 0.22)	*No reliable evidence of an association* There was no difference in the likelihood of developing depressive symptoms between those who drank more than or less than 14 g alcohol per day.	Important
Bipolar disorder	N=7,981 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Abstinent vs non-HED: ORs=1.22 (0.78, 1.91) and 1.16 (0.58, 2.32)	*No evidence of an association* A single large study reported that there was no difference in likelihood of incident bipolar disorder in women who were abstinent vs women who drank without participating in HED.	Important
				HED vs non-HED: ORs between 0.78 (0.25, 2.44) and 2.05 (0.83, 5.03)	*No evidence of an association* There was no difference in likelihood of incident bipolar disorder in women who participated in HED vs women who drank without HED.	Important
Suicide	N=0 K=0					Important
Anxiety	N=7,981 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Abstinent vs non-HED: ORs=0.85 (0.49, 1.38) and 1.20 (0.88, 1.64)	*The evidence shows no association* There was no difference in risk of developing anxiety in those who are abstinent and those who drink without HED.	
				HED vs non-HED: ORs=0.50 (0.18, 1.39) to 2.25 (0.87, 5.80)	*No reliable evidence of an association* There was no difference in likelihood of developing an anxiety disorder in those who participated in HED vs those who drank without HED.	

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=7,987 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Abstinent vs non-HED: ORs=1.21 (0.80, 1.85) and 0.89 (0.49, 1.62)	*No reliable evidence of an association* There was no difference in risk of developing PTSD in those who are abstinent and those who drink without HED.	Important
				HED vs non-HED: ORs=0.63 (0.13, 2.99) to 2.67 (1.05, 6.84)	*Limited evidence of an association* One study (with no adjustments for multiple comparisons) reported that those who females who participated in HED less than once per month had a higher risk of developing PTSD than non-HED.	Important
Alcohol related psychoses	N=0 K=0					Important

Question: What is the effect of alcohol consumption on mental health outcomes?
Patient or population: Older male subgroup
Exposure: Light, moderate, heavy drinking, short term risk drinking, long term risk drinking, HED, monthly drinking
Reference group: Abstinence, light drinking, non-HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=22,873 K=5 prospective cohort studies (Gea et al. 2013a; Hiles et al. 2015; Tanaka et al. 2011) (Lang et al. 2007; Tait et al. 2012)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Light-moderate drinkers vs being abstinent: HR=0.51 (0.26, 1.00) ORs=0.54 (0.26, 1.13) to 1.35 (0.45, 4.08) Abstinent vs light drinkers: OR=1.47 (1.22, 1.78) and z=0.12 (-0.13, 0.37) Heavy, hazardous drinker vs abstainer:	*No reliable evidence of an association* Four out of five studies were consistent that there was no association between quantity of alcohol per day and likelihood of developing depression. The remaining study reported that older males who were completely abstinent had worse depression outcomes than those who were light drinkers.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
				HR=0.75 (0.39, 1.43) ORs=0.83 (0.20, 3.43) and 0.99 (0.46, 2.11)		
	N=13,453 K=2 prospective cohort studies (An & Xiang 2015; Bots et al. 2008)	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨁⊖	Heavy vs non-heavy drinking or abstinence: OR=0.64 (0.23, 1.80) HR=1.05 (0.95, 1.17)	*The evidence shows no association* When high consumption or frequent drinking was compared against low consumption or abstinence, there were no significant differences in the chance of having depression at follow-up.	Critical
	N=7,902 K=1 prospective cohort study (Tait et al. 2012)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Short term risk drinking (≥4 drinks/day) vs 0-2 drinks/day: OR=1.30 (1.06, 1.59), p<0.05 Long-term risk drinking vs 0-2 drinks/day: OR=0.99 (0.82, 1.19)	*Limited evidence of association* A single study reported that short-term risk drinkers (4 drinks/day) had a higher likelihood of depression than low risk drinkers (0-2 drinks/day). There was no significant difference in the odds of depression in those who drank between 2 and 4 drinks/day vs those who drank less than 2 per day.	Critical
	N=5,461 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	HED vs non-HED: ORs=0.94 (0.44, 2.03) and 1.27 (0.56, 2.86)	*No reliable evidence of an association* A single study reported no significant difference in the likelihood of depression in people who participated in HED (< or ≥monthly) vs those who did not.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	N=2,683 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	Monthly drinker vs abstainer: OR=0.7 (0.5, 0.9), p<0.05	*Limited evidence of an association* Older males who drank at least monthly were significantly less likely to have depression at follow-up than those who never drank.	Critical
Bipolar disorder	N=5,461 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Abstinent vs non-HED: ORs=1.22 (0.78, 1.91) and 1.16 (0.58, 2.32)	*No evidence of an association* A single large study reported that there was no difference in likelihood of incident bipolar disorder in men who were abstinent vs men who drank without participating in HED.	Important
				HED vs non-HED: ORs between 0.78 (0.25, 2.44) and 2.05 (0.83, 5.03)	*No evidence of an association* There was no difference in likelihood of incident bipolar disorder in men who participated in HED vs men who drank without HED.	Important
Suicide	N=0 K=0					Important
Anxiety	N=1,987 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Abstinence vs non-HED drinking: OR=0.85 (0.49, 1.48) HED vs non-HED drinking: <1 per month: OR=2.25 (0.87, 5.80) >1 per month: OR=0.88 (0.32, 2.42)	*The evidence shows no association* A single study reported no difference in likelihood of incident anxiety based on being abstinent, a HED or non-HED drinker.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=5,461 K=1 prospective cohort study (Chou, Liang & Mackenzie 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⊖⊖	Abstinent vs non-HED: ORs=1.21 (0.80, 1.85) and 0.89 (0.49, 1.62)	*No reliable evidence of an association* There was no difference in risk of developing PTSD in those who are abstinent and those who drink without HED.	Important
				HED vs non-HED: ORs=0.63 (0.13, 2.99) to 2.67 (1.05, 6.84)	*No reliable evidence of an association* There were no significant differences for males.	Important
Alcohol related psychoses	N=0 K=0					Important

GRADE evidence profiles for people with existing mental and physical illnesses

Question: What is the effect of alcohol on mental health outcomes of someone with unipolar depression?
Patient or population: Youth with existing mental illness (adolescents with depressive disorders)
Exposure: Excessive use of alcohol (weekly drunkenness, or consuming typically more than 7 (females) or 10 (males) units/session).
Reference group: No/occasional use of alcohol.

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Remission of depression (BDI<10)	N=197 K=1 prospective cohort study (Meririnne et al. 2010)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊖⊖	HED vs no/occasional HR=0.49 (0.27, 0.89), p=0.020	*Limited evidence of an association* Participants of HED had less likelihood of their depression remitting than those who drank less than monthly and with no HED.	Critical
				Regular users vs no/occasional HR=1.02 (0.71, 1.47), p=0.90	*No reliable evidence of an association* Regular drinkers did not show any differences in rate of remission compared to no/occasional drinkers.	Critical
Alcohol related psychoses	N=0 K=0					Important

Question: What is the effect of alcohol consumption in those with existing mental illnesses on mental health outcomes?
Patient or population: Adults with bipolar disorder
Exposure: Frequency of alcohol use, number of drinks consumed daily, or any alcohol consumption
Reference group: (not applicable for continuous outcomes), or no alcohol consumption

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depressive episode	N=418 K=3 prospective cohort studies (Baethge et al. 2008; Jaffee et al. 2009; van Zaane et al. 2014)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Days of alcohol use: OR=1.036 (1.010, 1.062) Time to transition to depression: HRs=1.03 (0.97, 1.11) and 0.97 (0.82, 1.24) Regression coefficient for no. of drinks: 0.058; 95%CI 0.015, 0.100; z-score 2.67, p=0.007	*No reliable evidence of an association* There was conflicting evidence on the relationship between alcohol consumption and depressive episodes in people with bipolar disorder. Two out of three studies showed that alcohol use was associated with later depressive episodes, whereas one study showed that alcohol did not influence the time to transition to a depressive episode for either males or females.	Important
Manic episode	N=303 K=2 prospective cohort studies (Baethge et al. 2008; van Zaane et al. 2014)	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Time to transition to mania: HRs=0.81 (0.71, 0.92) males; 1.01 (0.85, 1.18) females Regression coefficient for no. of drinks: -0.014 to 0.011; z-scores -0.74 to 0.64, p=0.046-0.59	*No reliable evidence of an association* One small study reported that males who increased their weekly consumption by one drink per week had a longer time transitioning to a manic state. However, the same was not found for females. A second study found no relationship between alcohol and transition to manic or hypermania.	Important
Anxiety	N=0 K=0					Critical
Alcohol related psychoses	N=0 K=0					

Question: What is the effect of alcohol consumption in those with other physical illnesses on mental health outcomes?
Patient or population: Adults with and without HIV

Exposure: Hazardous drinking, HED or heavy drinking
Reference group: Non-hazardous drinking

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=2,446 K=1 prospective cohort study (Sullivan et al. 2011)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Hazardous drinking: OR=2.53 (1.34, 4.81), p<0.001 HED: OR=2.14 (1.49, 3.07), p<0.001 Interaction between alcohol-related categories and HIV status: OR=0.99 (0.83, 1.18), p=0.88	*There is evidence of an association* Veterans with and without HIV had a significantly higher risk of MDD after 6 years if they were hazardous drinkers or participated in HED compared with non-hazardous drinkers. HIV status did not influence the relationship between alcohol and depression.	Critical
Depressive symptoms	N=391 K=1 prospective cohort study (Sullivan et al. 2008)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊕⊕⊖	Mean difference on CES-D (range 0-60): 1.04 (-0.24, 2.32), p=0.11	*The evidence shows no association* While unadjusted mean CES-D scores were significantly higher for heavy drinkers compared to those who were not current heavy drinkers, the differences decreased after adjustments to be too small to be either clinically or statistically significant.	Important
Suicidal ideation	N=471 K=1 cross-sectional study (Lawrence et al. 2010)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Low risk vs no risk on AUDIT-C: OR=1.43 (0.86, 2.38) High risk vs no risk on AUDIT-C: OR=1.14 (0.61, 2.14)	*No reliable evidence of an association* A single small study reported no significant difference in risk of suicidal ideation between different AUDIT-C risk categories, after adjustments for confounders were made.	Important
Anxiety	N=0					Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
	K=0					
Alcohol related psychoses	N=0 K=0					Important

GRADE evidence profiles for people with existing alcohol dependence

Question: What is the effect of alcohol on the mental health of people with alcohol dependence?
Patient or population: People with existing alcohol dependence
Exposure: Alcohol consumption or pattern of consumption
Reference group: Another level or pattern of consumption
Author(s): No studies

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=0 K=0			No studies identified		Critical
Anxiety	N=0 K=0			No studies identified		Critical
Alcohol related psychoses	N=0 K=0					Important

GRADE evidence profiles for people with strong family history of alcohol dependence

Question: What is the effect of alcohol on the mental health of people with a strong family history of alcohol dependence?
Patient or population: People with a strong family history of alcohol dependence
Exposure: Alcohol consumption or pattern of consumption

Reference group: Another level or pattern of consumption
Author(s): No studies

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=0 K=0			No studies identified		Critical
Anxiety	N=0 K=0			No studies identified		Critical
Alcohol related psychoses	N=0 K=0					Important

GRADE evidence profiles for people on medicines or other drugs

Question: What is the effect of alcohol combined with other drugs on mental health?
Patient or population: Youth on other drugs (starting in adolescence), or
Exposure: Chronic, moderate-to-heavy cigarette, alcohol and marijuana use / Use of all three substances, or other drugs
Reference group: Occasional alcohol alone, neither drugs or alcohol
Author(s): (Brook, Judith S. et al. 2014; Brook, J. S. et al. 2016; Conner et al. 2017)

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Major depressive episode (within 23 years)	N=806 K=1 prospective cohort study (Brook, J. S. et al. 2016)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 1 but not rated up due to risk of bias Large effect: 0	⊕⊖⊖⊖	Chronic, moderate-to-heavy cigarette, alcohol and marijuana use vs occasional alcohol use only OR=2.67 (95%CI 1.14, 6.26)	*Limited evidence of an association* A trajectory of chronic, moderate-to-heavy cigarette, alcohol and marijuana use from adolescence to adulthood is associated with a higher risk of major depressive episode over the subsequent 23 years.	Critical

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
		Confounding: 0				
Generalised anxiety disorder (13-23 years)	N=1622 K=2 prospective cohorts studies (Brook, Judith S. et al. 2014; Brook, J. S. et al. 2016)	Risk of bias: -2 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0 Dose-response: 1 but not rated up due to risk of bias Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Chronic, moderate-to-heavy cigarette, alcohol and marijuana use vs occasional alcohol use only OR=6.39 (2.62, 15.56) and OR=2.22 (1.33, 3.70)	*Limited evidence of an association* Combined use of cigarettes, alcohol and marijuana is associated with a higher risk of a generalised anxiety disorder over 13 to 23 years.	Critical
Alcohol related psychoses	N=0 K=0					Important
Suicide	N=346 K=1 case control study (Conner et al. 2017)	Risk of bias: -1 Inconsistency: N/A Indirectness: -1 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	OR of dying by suicide rather than motor vehicle accident if blood toxicology showed alcohol alone or in combination with other drug: Alcohol alone vs neither: OR=1.22 (0.74, 2.00) Alcohol plus drug vs neither: OR=4.33 (1.70, 11.03), p<0.05 Drug alone vs neither: OR=1.03 (0.37, 2.88)	*Limited evidence of an association* Adults (aged 18-54) who had alcohol and drugs in their blood stream, were more likely to die by suicide than motor vehicle accident than if they had neither in their blood. The odds of the death being by suicide rather than motor vehicle accident was stronger when both alcohol and drugs were used (OR=4.33) than when drugs alone were use (OR=1.03) or alcohol alone was used (OR=1.22).	Important

Question: What is the effect of alcohol in those dependent on alcohol or other drugs on mental health?

Patient or population: Adults with dependence on either alcohol or other drugs
Exposure: Hazardous drinking (no. of occasions drinking ≥4 drinks/day for women, or ≥5 drinks/day for men, per month)
Reference group: No hazardous drinking

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=0 K=0	N/A				Critical
Depressive symptoms	N=307 K=1 prospective cohort study (Bahorik et al. 2016)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0	⊕⊕⊖⊖	Number of hazardous drinking day per month ß(SE)=0.10 (0.03), t=2.84, p=0.004	*Limited evidence of an association* For every additional hazardous drinking occasion per month, there was a 10% increase in depressive symptoms at follow-up.	Important
Anxiety	N=0 K=0	N/A				Critical
Anxiety symptoms	N=307 K=1 prospective cohort study (Bahorik et al. 2016)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0	⊕⊕⊖⊖	Number of hazardous drinking day per month ß(SE)=0.09 (0.03), t=2.79, p=0.005	*Limited evidence of an association* For every additional hazardous drinking occasion per month, there was a 9% increase in anxiety symptoms at follow-up.	Important
Alcohol related psychoses	N=0 K=0					Important
Evidence statement: *There was evidence that in adults with dependence (either alcohol or drugs), drinking at hazardous levels increases the risk of depressive symptoms and anxiety symptoms (GRADE ⊕⊕⊕⊖).*						

GRADE evidence profiles for people exposed to trauma

Question: What is the effect of alcohol on mental health outcomes in people exposed to trauma?
Patient or population: Adults exposed to traumatic injuries
Exposure: High or low pre-trauma consumption or problem drinking (AUDIT-C) or post-trauma number of drinks consumed
Reference group: Moderate pre-trauma moderate consumption, non-problem drinking

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD symptoms	N=3,807 K=2 prospective cohort studies (Hruska et al. 2017; Powers, MB et al. 2014)	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨀⨀⨀	Immediate post-trauma blood alcohol screen: OR=0.65	*No reliable evidence of an association* Blood alcohol concentration did not significantly predict PTSD symptoms 3 months later.	Important
				Post-trauma alcohol consumption: ß=0.01 (95%CI -0.01, 0.02)	*No reliable evidence of an association* Post-trauma alcohol consumption was not associated with next day PTSD symptoms.	Important
Anxiety symptoms	N=0 K=0					
Depression	N=1,035 K=1 prospective cohort study (Hoffman et al. 2011)	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⨁⨁⨀	Post-trauma alcohol: No unsafe use of alcohol: OR=1.0 (Reference) Reducing unsafe use: OR=2.95 (95%CI 1.28, 6.79) Beginning unsafe use: OR=1.47 (95%CI 0.62, 3.50) Continued unsafe use: OR=0.28 (95%CI 0.04, 2.18)	*Evidence of an association* Those who reduced their unsafe alcohol use after a spinal cord injury were more likely to have depression at follow-up.	Critical
Alcohol related	N=0					Important

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
psychoses	K=0					

Question: What is the effect of alcohol on mental health outcomes in people exposed to trauma?
Patient or population: Adults exposed to terrorism
Exposure: HED, drinks/day, and drinks/month
Reference group: No HED

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=1,681 K=1 prospective cohort study (Boscarino et al. 2011)	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	HED: ß(SE)=0.09 (0.04), p=0.018 Drinks/drinking day: ß(SE)=0.29 (0.13), p=0.023 Drinks/month: ß(SE)=0.13 (0.07), p=0.066	*No reliable evidence of an association* Alcohol use in the year prior to and after the World Centre Attacks was associated with PTSD 2 years after the attacks.	Important
Depression	N=0 K=0					Critical
Anxiety	N=0 K=0					Critical
Alcohol related psychoses	N=0 K=0					Important

Question: What is the effect of alcohol on mental health outcomes in people exposed to trauma?
Patient or population: Adult Defence Force personnel or Veterans
Exposure: Different alcohol trajectories or level of alcohol use, or hazardous drinking

Reference group: Average drinkers or non-hazardous drinkers

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
PTSD	N=512 K=1 prospective cohort study (Schultz, Glickman & Eisen 2014)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Alcohol use at T1: estimate(SE): -0.04 (0.13), NS	*No reliable evidence of an association* No statistically significant effects of alcohol trajectory or use at baseline on future likelihood of PTSD.	Important
PTSD symptoms	N=505 K=1 prospective cohort study (Goodwin et al. 2017)	Risk of bias: -2 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⊕⊖⊖⊖	Pre-trauma alcohol: Mean Difference in PCL-C score=0.10 (95%CI -0.04, 0.24), p=0.18 Post-trauma alcohol: Mean Difference in PCL-C score=0.04 (95%CI -0.17, 0.24), p=0.73	*No reliable evidence of an association* Pre- or post-trauma alcohol use did not predict PTSD symptoms at follow-up.	Important
Anxiety	N=0 K=0					Critical
Alcohol related psychoses	N=0 K=0					Important

Question: What is the effect of alcohol on mental health outcomes in people exposed to trauma?
Patient or population: Adult college students exposed to trauma or women exposed to sexual assault
Exposure: Alcohol quantity, peak drinking (greatest amount consumed in one occasion)

Reference group: alcohol quantity, peak drinking (continuous variable)

Outcomes	Participants Studies	Quality of evidence	GRADE	Results	Interpretation	Importance
Depression	N=0 K=0					Critical
Anxiety	N=0 K=0					Critical
PTSD symptoms	N=798 K=2 prospective cohort studies (Kaysen et al. 2011; Read et al. 2016)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Publication bias: 0 Dose-response: 0 Large effect: 0 Confounding: 0	⨁⊖⊖⊖	Pre-assault peak drinking x time: *B*=1.65 (-1.63, 4.93) Post-trauma: In cross-lagged panel model including alcohol use, PTSD symptoms, coping and alcohol consequences, alcohol use did not have any significant direct or indirect associations with PTSD symptoms.	*No reliable evidence of an association* One study reported that peak alcohol consumption prior to the trauma had no effect on PTSD symptoms over the follow-up period. Another study reported that post-trauma alcohol consumption was highly correlated with PTSD symptoms, but in an adjusted model, these associations were no longer significant.	Important
Suicide	N=0 K=0					Important
Alcohol related psychoses	N=0 K=0					Important

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8 Appendix A

2016 NHMRC Standards for Guidelines

1. To be relevant and useful for decision making guidelines will:
   1.1 Address a health issue of importance
   1.2 Clearly state the purpose of the guideline and the context in which it will be applied
   1.3 Be informed by public consultation
   1.4 Be feasible to implement

2. To be transparent guidelines will make publicly available:
   2.1 The details of all processes and procedures used to develop the guideline
   2.2 The source evidence
   2.3 The declarations of interest of members of the guideline development group and information on how any conflicts of interest were managed
   2.4 All sources of funding for the guideline

3. The guideline development group will:
   3.1 Be composed of an appropriate mix of expertise and experience, including relevant end users
   3.2 Have clearly defined, documented processes for reaching consensus

4. To identify and manage conflicts of interest guideline developers will:
   4.1 Require all interests of all guideline development group members to be declared
   4.2 Establish a process for determining if a declared interest represents a conflict of interest, and how a conflict of interest will be managed

5. To be focused on health and related outcomes guidelines will:
   5.1 Be developed around explicitly defined clinical or public health questions
   5.2 Address outcomes that are relevant to the guideline's expected end users
   5.3 Clearly define the outcomes considered to be important to the person/s who will be affected by the decision, and prioritise these outcomes

6. To be evidence informed guidelines will:
   6.1 Be informed by well conducted systematic reviews
   6.2 Consider the body of evidence for each outcome (including the quality of that evidence) and other factors that influence the process of making recommendations including benefits and harms, values and preferences, resource use and acceptability
   6.3 Be subjected to appropriate peer review

7. To make actionable recommendations guidelines will:
   7.1 Discuss the options for action
   7.2 Clearly articulate what the recommended course of action is, and when it should be taken
   7.3 Clearly articulate what the intervention is so it can be implemented
   7.4 Clearly link each recommendation to the evidence that supports it
   7.5 Grade the strength of each recommendation

8. To be up-to-date guidelines will:
   8.1 Ensure that the recommendation is based on an up-to-date body of evidence
   8.2 Propose a date by which the evidence and the guideline should be updated. This may be specific to each recommendation

9. To be accessible guidelines will:
   9.1 Be easy to find
   9.2 Ideally be free of charge to the end user
   9.3 Be clearly structured, easy to navigate and in plain English
   9.4 Be available online