Cochrane Australia

Systematic review of the association between different levels and patterns of alcohol consumption and long-term mild cognitive impairment

Technical report prepared by Cochrane Australia

26 November 2018

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Contents

Scope of the technical report

The Technical Report includes a complete description of the methods for the review (with section numbering matching that used in the main report), and appendices providing additional methods detail (Appendix 1. database search strategies, Appendix 2. data manipulation) and description of changes to protocol (Appendix 3). Other appendices report additional characteristics of included and excluded studies (Appendices 4, 5, 6, 8 and 9), results from sensitivity analyses (Appendix 7), abbreviations used in the review (Appendix 10), and a full response to comments and actions arising from the independent methodological review (Appendix 11).

3. Methods

Methods reported in this review are based on the *Cochrane Handbook for Systematic Reviews of Interventions* [1], with modifications for undertaking a review of exposures. The GRADE approach is used to summarise and assess the certainty of evidence arising from the review (see Section 3.3.9 for details). GRADE methods are widely used in guideline development to ensure a systematic, transparent and common approach to interpreting results [2]. The review is reported in accordance with the PRISMA statement [3, 4], with additional methods description based on the PRISMA-P statement [5, 6].

3.1 Criteria for considering studies for this review

3.1.1 Types of participants

General population

Studies that were limited to one or more of the following subgroups were eligible for inclusion:

- People in specific age groups identified in the 2009 *Alcohol guideline* as potentially having a higher risk of harm from alcohol exposure than the general population. For example, children and young people (less than 18 years), young adults (18-25), older people (65 and over)
- Women or men

We planned to report data and analyses from studies that met other eligibility criteria for the following subgroups.

- people with existing health conditions (physical, mental or both)
- people using licit and/or illicit drugs
- people with a family history of alcohol dependence.

Studies restricted to one or more of these three subgroups were eligible only if the study explicitly aimed to examine the association between alcohol consumption and long-term cognition.

3.1.2 Types of exposure

Eligible studies were those examining different levels of alcohol consumption, patterns of alcohol consumption, or both.

Measurement methods and quantification: Studies were eligible irrespective of the methods used to measure alcohol exposure. We anticipated that these methods would vary across studies, but would include retrospective survey involving recall of alcohol consumption over different periods of life or intake diaries to measure current alcohol consumption. Single or repeated measures of exposure were eligible. Studies had to report alcohol consumption in units that allowed quantification of the average amount of alcohol consumed (e.g. grams or millilitres of pure alcohol) over a period of time (e.g. per day, week, month).

Timing of alcohol exposure measurement. The timing of measurement needed to match the study design features listed in section 3.1.5 for a prospective design. Data collected on alcohol consumption, and used in analyses, had to be collected at least six months prior to the first follow-up measure of cognition. Concurrent measures of alcohol were accepted only in studies with multiple measures of alcohol over time, where the final measure was taken concurrently with a baseline (not follow-up) measure of cognition.

To account for differences in the methods used to measure alcohol exposure, we extracted data on the measurement methods and assessed potential biases that may arise through the method used.

3.1.3 Types of comparator exposure

For inclusion in the review, the comparator group must have been a different level or pattern of alcohol consumption.

For inclusion in the meta-analysis of different levels of alcohol consumption and the dose-response analysis, studies had to report results for either a 'never' drinker group or a 'very low-level' drinker group. We broadly defined 'never' drinkers as individuals that had never consumed a serve of alcohol (lifetime abstainers) or had consumed very little alcohol across their lifetime. Where lifetime consumption was not measured, we accepted current non-drinkers (e.g. based on consumption over the preceding 12 months), noting in data extraction and risk of bias assessment the potential for misclassification and contamination of a non-drinking group with former drinkers. A similar approach was taken to misclassification of occasional drinkers, where the recall period was such that occasional drinkers might be missed and incorrectly categorised as non-drinkers. We defined very low-level drinkers as those whose average alcohol consumption was zero to <10 g/week. The latter threshold reflects consumption of a single Australian standard drink (10 grams of alcohol).

We anticipated diversity across studies in the definition and composition of potentially eligible comparator groups (which may or may not be the referent group to which other categories of alcohol consumption were compared in each study) [7]. For example, across studies referent groups have been defined as never drinking [8], not drinking above a certain threshold (e.g. less than one unit of alcohol per week [9]), and not drinking over a defined period of time (e.g. less than one unit over the preceding 12 months [10]). Studies reporting a group with these or similarly low levels of alcohol consumption were eligible, irrespective of whether the group was used as the referent in the study.

3.1.4 Types of outcomes

Eligible studies were those that reported at least one measure of cognitive function (or performance), which is the primary outcome for this review. Studies must have assessed cumulative long-term effects of alcohol consumption on cognitive function (e.g. decline in function over time). We excluded studies that only examined acute effects (during intoxication or withdrawal), long-term effects arising from injury on a single drinking occasion (e.g. a traumatic brain injury sustained while

intoxicated), and those where there was insufficient length of follow-up to examine the longer-term effects of cumulative exposure (< 6 months). While we did not set a minimum threshold for 'long-term', we considered the extent to which studies provided evidence of a sustained effect, and the duration of this effect, when interpreting results (see *Timing of outcome measurement*). We also excluded studies that only examined cognitive function as a predictor of alcohol-use behaviours (e.g. studies examining whether prior cognitive function led to heavy alcohol use).

Eligible outcomes were broadly categorised as follows.

Cognitive function

- global cognitive function
- domain-specific cognitive function (especially domains that reflect specific alcohol-related neuropathologies, such as psychomotor speed and working memory)

Clinical diagnoses of cognitive impairment

- mild cognitive impairment (also referred to as mild neurocognitive disorders)

These conditions were "characterised by a decline from a previously attained cognitive level" ([11], p2675).

Major cognitive impairment (also referred to as major neurocognitive disorders; including dementia) was excluded.

We expected that definitions and diagnostic criteria would vary across studies, so accepted a range of definitions as noted under *Methods of outcome assessment*. Table 1 provides an example of specific domains of cognitive function used in the diagnosis of mild and major cognitive impairment in the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) [12]).

Table 1. Domains used to diagnose major and mild neurocognitive disorders in the DSM-5

Domain	Cognitive abilities covered by the domain
Complex attention	sustained attention, divided attention, selective attention, processing
Executive function	planning, decision making, working memory, responding to feedback/error correction, overriding habits, mental flexibility
Learning and memory	immediate memory, recent memory
Language	expressive language and receptive language
Perceptual-motor ability	construction and visual perception
Social cognition	recognition of emotions, theory of mind, behavioural regulation

Methods of outcome assessment

Any measure of cognitive function was eligible for inclusion. The tests or diagnostic criteria used in each study should have had evidence of validity and reliability for the assessment of mild cognitive impairment, but studies were not excluded on this basis.

We anticipated that many different methods would be used to assess cognitive functioning across studies. These include the following.

Clinical diagnoses of

- mild cognitive impairment using explicit criteria (e.g. [13], National Institute on Aging and the Alzheimer's Association (United States; NIA-AA) criteria [14]; any of the definitions of mild cognitive impairment described in [15])

Neuropsychological tests used to assess global cognitive function, for example the:

- Mini Mental State Examination (MMSE)
- Addenbrooke's Cognitive Examination - Revised (ACE-R) which "incorporates the MMSE and assesses attention, orientation, fluency, language, visuospatial function, and memory, yielding subscale scores for each domain" [16]
- Montreal Cognitive Assessment (MOCA), which provides measures for specific cognitive abilities and may be more suitable for assessing mild cognitive impairment than the MMSE [16]

Neuropsychological tests for assessing domain-specific cognitive function, for example tests of:

- attention and processing speed, for example the Trail making test (TMT-A)
- memory, for example the Hopkins verbal learning test (HVLT-R; immediate, delay)
- visuospatial ability, for example the Block design test
- executive function, for example the Controlled Oral Word Association Test (COWAT)

Results could be reported as an overall test score that provides a composite measure across multiple areas of cognitive ability (i.e. global cognitive function), sub-scales that provide a measure of domain-specific cognitive function or cognitive abilities (e.g. processing speed, memory), or both.

Timing of outcome measurement

Studies with a minimum follow up of six months were eligible. This threshold was based on previous reviews examining the association between long-term cognitive impairment and alcohol consumption (e.g. Anstey 2009 specified 12 months [17]) and guidance from the Cochrane Dementia and Cochrane Improvement Group, which suggests a minimum follow-up of nine months for studies examining progression from mild cognitive impairment to dementia [16]. We deliberately specified a shorter period to ensure studies reporting important long-term effects were not missed.

No restrictions were placed on the number of points at which the outcome was measured, but the length of follow up and number of measurement points (including a baseline measure of cognition) was considered when interpreting study findings and in deciding which outcomes were similar enough to combine for synthesis. Since long-term cognitive impairment is characterised as a decline from a previous level of cognitive function and implies a persistent effect, studies with longer-term outcome follow up at multiple time points should provide the most direct evidence.

Selection of cognitive outcomes where multiple are reported

We anticipated that individual studies would report data for multiple cognitive outcomes.

Specifically, a single study may report results:

- for *multiple constructs* related to cognitive function, for example global cognitive function and cognitive ability on specific domains (e.g. memory, attention, problem-solving, language);
- using *multiple methods or tools to measure* the same or similar outcome, for example reporting measures of global cognitive function using both the MMSE and the MOCA;
- at *multiple time points*, for example at one, five and 10 years.

Where multiple cognition outcomes were reported, we selected one outcome for inclusion in analyses and for reporting the main outcomes (e.g. for GRADEing), choosing the result that provided the most complete information for analysis. Where multiple results remained, we listed all available outcomes (without results) and asked our content expert to independently rank these based on relevance to the review question, and the validity and reliability of the measures used. Measures of global cognitive function were prioritised, followed by measures of memory, then executive function. Methods for selecting results when there are multiple effect estimates and/or analyses are described in Sections 3.3.4 and 3.3.9.

Secondary outcomes

We planned to include studies that reported brain structure outcomes (as measured by neuroimaging) only if the study also reported a cognitive function outcome (i.e. studies reporting only a brain structure outcome with no measure of cognitive function were excluded).

Excluded outcomes

In line with recommendations from the Cochrane Dementia and Cognitive Improvement Group [18], surrogate outcomes were ineligible, for example:

- brain structure and function, in the absence of a measure of cognitive function
- biomarkers

3.1.5 Types of studies

Cohort studies and nested case-control studies were eligible for inclusion in the review.

Broadly, these types of designs can be described as follows.

- *Cohort*: "a study in which a defined group of people (the cohort) is followed over time, to examine associations between different … [exposures] and subsequent outcomes" [19].
- *Nested case-control*: a study in which "Individuals experiencing an outcome of interest are identified from within a defined cohort (for which some data have already been collected) and form a group of 'cases'. Individuals, often matched to the cases, who did not experience the outcome of interest are also identified from within the defined cohort and form the group of 'controls'." Data characterising prior exposure "are collected retrospectively". [19]. Data on alcohol exposure should be collected from existing records, since those experiencing cognitive decline may not to be able to provide sufficiently valid and reliable information about their prior exposure.

In line with current Cochrane guidance, decisions about study eligibility were based on assessment of the study design features listed in Table 2 rather than labels ('cohort' or 'case-control') or broad definitions of each type of study.

Definition of study 'baseline'. Prospective assessment of alcohol consumption (Table 2, design feature 3b) was judged to have occurred if data on alcohol consumption was collected at least six months prior to the first 'follow-up' measure of cognition. We defined the last point at which alcohol was measured as the 'baseline' for the study (an important consideration for studies with alcohol consumption data collected at multiple time points). A 'baseline' assessment of cognition may have been made at this point, but was not a requirement for inclusion in the review (Table 2, design feature 3c). Studies that collected alcohol data concomitantly with follow-up measures of cognition (i.e. beyond 'baseline') were excluded unless they reported an analysis based only on the alcohol measures taken prospectively. To avoid ambiguity when describing data collection points, we used a standardised nomenclature for each point (T0 being the first measurement point, then each subsequent point numbered sequentially: T1, T2, T3, etc.).

Table 2. Design features for determining study eligibility (adapted from [19])

Study design feature	Prospective cohort	Retrospective cohort	Nested case-control
(1a) A comparison between two or more groups of participants with different levels or patterns of alcohol consumption ('yes' = cohort or NCC)	Yes	Yes	Yes
(1b) A comparison within the same group of participants with different levels or patterns of alcohol exposure (one of which is no or low-level exposure) ('yes' = excluded design)	No	No	No
(2a) Participants were allocated to groups based on different levels or patterns of alcohol exposure	Yes	Yes	No (based on outcome)
(2b) Participants were allocated to groups on the basis of outcomes	No	No	Yes
(3) The following parts of the study were prospective:			
a. identification of participants	Yes	No	Yes
b. assessment of alcohol consumption and allocation to alcohol consumption categories prior to follow-up measures of cognition	Yes	No	Yes (from existing records)
c. assessment of outcomes (baseline cognition)	Yes	Possibly	Yes
d. generation of hypotheses	Yes	Yes	Yes
Assessment of comparability of groups was based on:			
• potential confounders	Possibly	Possibly	Possibly
• outcome variables at baseline	Possibly	Possibly	No

While eligible for this review, randomised trials examining the effects of different levels and/or patterns of alcohol exposure are unlikely to be conducted because of ethical concerns and the length of follow-up required to measure long-term cognitive outcomes.

Excluded designs. Case-control studies were excluded, except for nested case-controls. Case control studies compare "people with a specific outcome of interest ('cases') with people from the same source population but without that outcome ('controls'), to examine the association between the outcome and prior exposure" [19]. This design is unsuitable for addressing the objectives of this review, since it is unlikely to be possible to obtain valid and reliable estimates of prior exposure to alcohol from individuals with the outcome of interest (cognitive impairment).

Studies using other designs (before-after comparisons, cross-sectional studies) were excluded since it is difficult (if not impossible) to attribute observed changes in outcomes to the exposure [19]. Studies that collected longitudinal data, but only presented analyses based on concomitant measures of alcohol and cognition, were also excluded on this basis.

Date and language restrictions. Studies published from 2007 onwards were eligible for inclusion. Studies published in languages other than English were excluded. A recent study has shown that the exclusion of studies in languages other than English rarely impacts on the results and conclusion of a review [20], a finding that is consistent with an earlier study that found no evidence that English-language restriction introduces systematic bias in meta-analytic results [21].

3.2 Search methods for identification of studies

Our approach combined searching for systematic reviews as well as primary studies. Searches were limited to bibliographic databases and checking the reference lists of eligible studies.

3.2.1 Systematic reviews

The independent evidence evaluation on the health effects of alcohol consumption commissioned by NHMRC [22] listed 13 systematic reviews (published between 2007 and 2016) that related to alcohol and cognitive impairment. From these reviews we retrieved all primary studies that met the eligibility criteria. In addition, we searched MEDLINE and Embase for systematic reviews published since 2016, and ensured that any relevant primary studies included in these reviews were considered for inclusion.

3.2.2 Primary studies

The primary studies we identified from existing systematic reviews served as the initial source of studies. We used information about how these studies were indexed (i.e. thesaurus terms, text words) to help develop and validate the search strategy for primary studies. This technique (referred to as relative recall) is particularly useful when there are a reasonable number of studies (~20).

Independently of the search for systematic reviews, we searched for primary studies relevant to the review question published since January 2007. No language or geographic limitations were applied to the search. Searches were limited to MEDLINE, Embase and PsycINFO.

The search strategy for Ovid MEDLINE was based on an assessment of the 2009 systematic review by Anstey [17] and the more recent 2017 meta-analysis by Xu [23]. The searches conducted for the Anstey review were very broad, generating over 33,000 citations, of which 15 were ultimately included in the meta-analysis. The MEDLINE search (see Technical report, Appendix 1) retrieved all the studies included in the Anstey review but is considerably more precise. This search also retrieved all seven additional studies included in the meta-analysis by Xu.

We decided not to include the text word 'impairment' as a stand-alone term since records retrieved using this text word (not already retrieved by the text words 'cognition' or 'cognitive') were mostly concerned with kidney or liver impairment, or some other impairment, and unrelated to cognition.

The MEDLINE search was translated for Embase and PsycINFO, incorporating each database's relevant thesaurus terms for alcohol, dementia/cognitive impairment and study design (see Technical report, Appendix 1).

Beyond database searching, we checked the reference lists of eligible studies for additional relevant publications.

3.3 Data collection and analysis

3.3.1 Selection of studies

Citations identified from the literature searches and reference list checking were imported to EndNote and duplicates removed. Three reviewers independently screened a sample of 109 citations to pre-test and refine coding guidance based on the inclusion criteria. Disagreements about eligibility were resolved through discussion. One reviewer (SB, JR or SM) then each screened about a third of the remaining citations (grouped by year of publication) for inclusion in the review using the pre-tested coding guidance.

Full-text of all potentially eligible studies were retrieved. A sample of full-text studies was independently screened by two reviewers (SB and JR) until concordance was achieved (~15%; 37/228 of full-text studies screened). The remaining full-text studies were screened by one reviewer (SB or JR). All included studies, and those for which eligibility was uncertain, were screened by a second reviewer (JR or SB). Disagreements or uncertainty about eligibility were resolved through discussion, with advice from the review biostatisticians (JM, AF or both) to confirm eligibility based on study design and analysis methods. Further information was sought from authors of two studies (Piumatti 2018, Wardzala 2018) to clarify methods and interpretation of the analysis.

Citations that did not meet the inclusion criteria were excluded and the reason for exclusion was recorded at full-text screening.

Cohort names, author names, and study locations, dates and samples characteristics were used to identify multiple reports arising from the same study (deemed to be a 'cohort'). These reports were matched, and data extracted only from the report that provided the most relevant analysis and complete information for the review. In most cases, the decision was based on the outcome reported (global function was prioritised).

3.3.2 Data extraction and management

For each included study, one review author (SB, JR or JM) extracted data relating to study characteristics using a pre-tested data extraction and coding form. A second author (SB, JR or JM) independently verified data relating to alcohol consumption categories (including conversions to grams per day) and outcome measures. One author extracted quantitative data (JM). Discrepancies were resolved through discussion, and advice sought from the review content expert (SW) or biostatistician (AF) if agreement could not be reached or for more complex scenarios.

Pre-testing of the data extraction and coding form was done on two studies purposefully selected from the included studies to cover the diversity of data types anticipated in the review. Advice was sought from the review content expert (SW) and biostatisticians (JM or AF) to ensure data were

extracted as planned. Revisions to the data extraction form were made as required to maximise the quality and consistency of data collection.

We extracted information relating to the characteristics of included studies and results as follows.

1. Study identifiers and characteristics of the study design

    - Study references (multiple publications arising from the same study were matched to an index reference, which is the study from which results were selected for analysis or summary)

    - Study or cohort name, location and commencement date

    - Study design (categorised as 'prospective cohort study', 'nested case-control study', or 'other' using the checklist of study design features developed by Reeves and colleagues, [19])

    - Funding sources and funder involvement in study.

2. Characteristics of the exposure and comparator groups

    - Levels of alcohol consumption as defined in the study, including details of how consumption was measured and categorised, and information required to convert data for reporting and analysis

        - qualitative descriptors of each category, if used (e.g. never or non-drinker, abstainer, former drinker, low/moderate/heavy consumption)

        - upper and lower boundaries of each category (e.g. 1 to 29 grams per day; 5.1 to 10 units per week based on a standard drink in the UK)

        - group used as referent category (comparator) in analyses and how defined

        - units of measurement (e.g. standard units of alcohol per day and definition of unit)

        - method of collecting alcohol consumption data (e.g. retrospective survey involving recall of alcohol consumption over different periods of life; intake diaries to measure current alcohol consumption); time points at which exposure data were collected

        - sample size for each exposure group at each measurement point and included in analysis; number lost to follow up [these data were used in the analysis and risk of bias assessment]

        - any additional parameters used to derive each category or exposure measure (e.g. alcohol consumption at each drinking occasion; frequency of drinking; recall period)

    - Patterns of exposure

        - Any additional data not listed above that characterises and quantifies different patterns of alcohol exposure (e.g. consumption on heaviest drinking day; diagnosis of an alcohol-use disorder such as dependence or harmful drinking, and the method of assessment; definition of other frequency-based categories used to characterise patterns of drinking such as occasional drinking or infrequent consumption).

    - Duration/length of exposure period at study baseline and follow-up (directly reported or data that can be used to calculate)

    - Age at commencement of drinking (initial exposure)

3. Characteristics of participants
    - Age at baseline and follow up, sex, ethnicity, co-morbidities, socio-economic status (including education), use of licit or illicit drugs, family history of alcohol dependence
    - Other characteristics of importance within the context of each study
    - Eligibility criteria used in the study
4. Outcomes assessed and results
    - Outcomes domains (e.g. cognition, brain structure, function in daily life)
    - For cognition outcomes:
        - Measurement method (e.g. Montreal cognitive assessment) and time points
        - Potential confounders, co-exposures and other sources of bias mentioned in the paper [24]. Baseline statistics of the confounders to allow assessment of the comparability of the exposure groups.
        - Results including: summary statistics (means and standard deviations, or number of events for cognitive outcomes that have been dichotomised, and sample size) in each exposure category, unadjusted and adjusted estimates of the associations (e.g. mean differences, confidence intervals, t-values, p-values, or risk ratios/odds ratios for binary outcomes) overall and stratified by the specified subpopulations, where possible. For adjusted estimates, we extracted information on the analysis method, how confounding was adjusted, and which confounders were adjusted for.
        - Data required to assess risk of bias (see Section 3.3.3) and report the methods that influenced judgements [24]. In particular, we collected and summarised information about study design features that potentially introduced selection bias (e.g. a lag time between initiating drinking and enrolment to the study), or bias through misclassification of alcohol consumption status (e.g. measures that do not capture variation in patterns of drinking over time).

3.3.3 Assessment of risk of bias of included studies

One author (MP) assessed risk of bias for each included study using ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool [25], and a second author (SB) independently verified the assessments and summarised study design features on which judgements were made. Discrepancies were resolved through discussion, with advice from a third reviewer (JM) if agreement could not be reached, for more complex scenarios or judgements of critical risk of bias (see below). To ensure concordance, the assessment process was piloted by all assessors (JM, SB and MP) on two included studies.

ROBINS-I was developed for "evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions" from non-randomised studies (i.e. where randomisation was not used to allocate individuals to comparison groups) [25]. While alcohol is generally considered an exposure, ROBINS-I has been successfully applied to equivalent studies (e.g. those examining the association between change in body size and mortality) and has advantages over checklist approaches in that it facilitates an overall judgement of RoB that can be incorporated in the analysis and the GRADE assessment [25, 26].

ROBINS-I requires assessment of the following seven domains:

1. Bias due to confounding
2. Bias in selection of participants into the study
3. Bias in classification of interventions (exposure)
4. Bias due to deviations from intended interventions (exposures)
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in selection of the reported result

It is recommended that users applying ROBINS-I should consider in advance the confounding factors and co-interventions that have the potential to lead to bias in included studies. These are listed at the end of this section.

Within each domain, we judged risk of bias as "low" (comparable to a well performed randomised trial), "moderate" (sound for a non-randomised study), "serious" (there are some important problems) or "critical" (the study is too problematic to provide useful evidence).

We rated the *overall risk of bias* for each result based on the most serious risk of bias judgement across any of the seven domains (i.e. overall risk of bias is "serious" if at least one domain is rated "serious"). If we judged a result to be at "critical" risk of bias on the first domain (bias due to confounding), we did not assess other domains, since the overall risk of bias for the result would be "critical" by default. Studies that were judged to be at "critical" risk of bias overall were excluded from the summary and syntheses of results, and they do not contribute to our conclusions. For each study and result (outcome) assessed, we report our judgment of risk of bias by domain and provide a rationale for the judgment with supporting information about study methods. Our risk of bias judgments are tabulated in the Technical report, Appendix 6.

Pre-specification of confounding factors and co-exposures

Confounding domains are "prognostic variables (factors that predict the outcome of interest)" that also predict the exposure at baseline [25]. ROBINS-I defines important confounding domains as those "for which, in the context of [a specific] study, adjustment is expected to lead to a clinically important change in the estimated effect of the [exposure]". We considered the following confounding domains as important for most or all studies since they have been shown to be associated with alcohol consumption and are prognostic factors for cognitive impairment: age, sex, socio-economic factors (especially education), smoking, and co-morbidities (especially diabetes, and obesity). Co-exposures were assessed on a study-by-study basis.

For GRADE assessments it was necessary to summarise risk of bias assessments across studies for each outcome. We followed recent GRADE guidance for making these judgements [26]. These summary assessments of risk of bias were used in determining the overall certainty of the body of evidence using GRADE, and the basis for each is reported as footnotes to the summary of findings tables.

3.3.4 Measures of association

Cognition was assessed using continuous measures with varying scales and neurocognitive tests across the studies. The standardised mean difference (SMD) was therefore used to standardise the associations so that they were comparable across studies. In some studies, the measures of cognition

were dichotomised and analysed as binary outcomes. These studies reported odds ratios along with 95% confidence intervals. For these studies, we converted the odds ratios (ORs) and their confidence limits to SMDs using a simple approximation proposed by Chinn [27]. The accuracy of the resulting SMD variances were assessed, and where necessary, adjustments were made to these variances so that when they were back transformed to the (log) OR scale, they yielded equivalent variances to the observed (log) OR variances. In the circumstance where results from multiple multivariable models were presented, we extracted associations from the most fully adjusted model, except in the case where an analysis adjusted for a possible intermediary along the causal pathway (i.e. post baseline measures of prognostic factors (e.g. smoking, drug use, hypertension)) [28].

3.3.5 Unit of analysis issues

In this review, the unit of analysis issue that arose was multiple estimates of association calculated for different levels of alcohol consumption within the same study. These estimates are correlated, since each level of alcohol consumption is compared against the same group of participants (i.e. current non-drinkers). Methods used to adjust for the correlation between the estimated associations are described in the *Data synthesis* section.

3.3.6 Assessment of heterogeneity

We assessed heterogeneity through visual inspection of the study-specific dose-response curves, formal testing for heterogeneity using the χ^2 test (using a significance level of $\alpha=0.1$), and quantified heterogeneity in the study-specific dose-response coefficients using the I^2 statistic.

3.3.7 Assessment of reporting biases

We had planned to investigate the potential for small study effects using contour-enhanced funnel plots and formal statistical tests for funnel plot asymmetry if there were at least 10 studies included in a synthesis. However, all syntheses included fewer than 10 studies.

3.3.8 Data synthesis

Investigation of the association between levels of alcohol consumption and cognition

We had planned to undertake meta-analyses of pairwise comparisons of levels of alcohol consumption (≥10 g/week and <10 g/day; ≥10 g/day and <20 g/day; ≥20 g/day and <30 g/day; ≥30 g/day and <40 g/day; ≥40 g/day and <50 g/day; ≥50 g/day) versus never drinkers or very low level drinkers (zero to <10 g/week). We did not undertake these analyses since all studies that contributed data suitable for synthesis were able to be included in the dose-response analyses. The dose-response analyses provide a more complete understanding of the relationship between alcohol consumption and the size of the SMDs, since all data are modelled in a single synthesis. Further, from these models, SMDs at any level of alcohol consumption (within the observed range) can be predicted.

Investigation of the dose-response relationship between levels of alcohol consumption and cognition

Analyses were undertaken to identify and characterise dose-response relationships between levels of alcohol consumption and cognition. For each study, the relationship between the SMD of cognition (compared with abstainers) and alcohol consumption was modelled using a restricted cubic spline with three knots (at the 10^{th}, 50^{th} and 90^{th} percentiles of alcohol consumption), accounting for correlation amongst the SMDs. The estimated study-specific dose-response coefficients and their covariance matrices were combined using a random effects multivariate model [29]. The between-

study variance of the dose-response coefficients was obtained using restricted maximum likelihood. Studies assessed as at a critical risk of bias were not included in the dose-response analysis.

In studies that reported alcohol consumption in different units (e.g. millilitres or standard drinks per days), we converted these to grams per day using the relevant country's standards [30]. For each category of alcohol consumption, we used the median or mean of alcohol consumption in grams per day when presented. When not presented, we assigned the midpoint of the category as the dose value. When the largest dose category was reported without an upper bound, the dose value assigned was calculated as the lower bound of the largest dose category plus the width of the previous (second-to-largest) category [31].

The combined does-response curves, along with 95% confidence intervals, were presented graphically and in tabular form (presenting predicted standardised mean differences of cognition for different alcohol consumption levels).

We examined the robustness of the combined dose-response model to different locations of the knots. We had also planned to examine the robustness of the combined dose-response model to different numbers of knots, but we did not do this. For each dose-response analysis we were limited to a maximum of three knots due to some studies only reporting three levels of alcohol consumption.

The dose-response models were fitted using the package `dosresmeta` in the statistical program R [32].

Subgroup analyses

We present the dose-response relationships for females and males separately where possible (i.e. where the study was undertaken with only one sex, or the results were reported separately by sex within a study). For other potential modifying factors (age, co-morbidities, drug taking, or a family history of alcohol use), no studies were limited to a particular subpopulation, nor did they report associations separately by particular subpopulations within a study.

Sensitivity analyses

We had planned to undertake sensitivity analyses examining the robustness of the results to the method of alcohol measurement (intake over multiple time points versus once) and limiting to studies that reported results for 'never' drinkers. We did not undertake these sensitivity analyses due to only a small number of studies available for any of the dose-response analyses (i.e. a maximum of six studies).

Summary of results from single studies

For studies that were not able to be included in the dose-response analyses, we summarised the risk of bias assessment, the study characteristics, the reported associations (including 95% confidence intervals and p-values where reported), and provided an interpretation. We had planned to present reported associations using forest plots, but because of incomplete reporting and the variability in the measures of association (e.g. linear trends, quadratic trends, hazard ratios, odds ratios) used across the studies, this was not possible.

3.3.9 Summary of findings tables and assessment of certainty of the body of evidence

We assessed the certainty of the evidence for results from the dose-response analysis using the GRADE approach. In accordance with the detailed GRADE guidance [2, 26], the following domains

were assessed (as briefly summarised below) and a judgement made about whether there were serious, very serious or no concerns in relation to each domain.

1. Risk of bias. Based on the summary assessment across studies for each outcome reported for a comparison (see 'Risk of bias' section). The assessment will be based on guidance for ROBINS-I [24] and GRADE [26].

2. Inconsistency. We assessed (1) whether there was heterogeneity in the observed effects across studies that suggested important differences in the effect of the exposure (based on visual inspection of data and statistical tests of heterogeneity), and (2) whether this could be explained (e.g. by variance in effects across subgroups if data were available).

3. Imprecision. We assessed whether interpretation of the upper and lower confidence limits leads to conflicting interpretations about the effect of the exposure (e.g. benefit and appreciable harm).

4. Indirectness. We assessed whether there were differences between the characteristics of included studies (PECO of included studies) and the review question (in terms of the review PECO) that such that the effects observed in the included studies were unlikely to apply directly to the review question. For example, studies with multiple measures of alcohol over time, and longer-term outcome follow up at multiple time points, were assessed as providing the most direct evidence of the cognitive effects of life-long alcohol-use patterns. This information was used to interpret results, rather than downgrade.

5. Publication bias. Our judgement of suspected publication bias was based on assessment of reporting bias as described in section 3.3.8. Evidence of small-study effects and the absence of a plausible alternative explanation for these effects indicates that publication bias should be suspected.

6. Upgrading domains (large effect size, dose-response gradient, opposing plausible residual confounding). Recent GRADE guidance is that observational studies may start as high certainty evidence when ROBINS-I is used for risk of bias assessment [26]. Doing so alters the assessment of GRADE upgrading domains, since these domains examine the likelihood that any observed association could be explained by residual confounding, and are typically used to upgrade observational studies from low to moderate or high certainty. In line with one of the options presented in recent GRADE guidance, we will consider these GRADE domains when assessing confounding in ROBINS-I.

GRADEpro GDT software (www.gradepro.org) was used to record decisions and derive an overall GRADE (high, moderate, low or very low) for the certainty of evidence for each outcome, using the GRADE rules in which observation studies assessed using ROBINS-I begin as 'high' certainty evidence (score=4) and can be downgraded by -1 for each domain with serious concerns or -2 for very serious concerns [26].

A summary of findings table (using the evidence profile format for guidelines) was prepared using the GRADEpro GDT software. For each result from the dose-response analysis, the evidence profile includes estimates of the effects of alcohol exposure reported as standardised mean differences, and the overall GRADE (rating of certainty). The evidence profile also includes (1) the study design(s), number of studies contributing data (the type and size of the evidence base), (2) our assessment of each of the domains (risk of bias, inconsistency, indirectness, imprecision, publication bias), and (3) a statement interpreting the evidence (clinical impact) for each outcome (by population subgroup). Footnotes are included to explain judgements made about downgrading the rating of the certainty of the evidence.

Evidence statements

Evidence statements were written for results from dose-response analyses. Formulation of the statements was based on the following decision-rules, as developed for the NHMRC. Information about the size and direction of association (referred to as effect [33]) was incorporated in the summary of findings.

Statement	Decision rule (based on GRADE ratings)
Consistent evidence of an association	High certainty evidence from two or more studies
Evidence of an association	High certainty evidence from one study OR Moderate certainty evidence from two or more studies
Consistent evidence of no association	High certainty evidence from two or more studies
Limited evidence of an association	Moderate certainty evidence from one study OR Low certainty evidence. OR Very low certainty evidence for a specific estimate, but where multiple studies showed a similar pattern of association
No reliable evidence of an association	Very low certainty evidence from only one study or from multiple studies where the pattern of association was inconsistent across studies

Appendices

Appendix 1. Database search strategies

Search strategy for systematic reviews (Embase and MEDLINE)

Embase Classic+Embase 1947 to 2018 February 12 and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to February 07, 2018

#	Search Statement	Results
1	exp Alcohol drinking/	106261
2	exp Alcoholic Beverages/	45653
3	Alcoholic intoxication/	18410
4	Alcoholism/	193695
5	exp Alcohol-Related Disorders/	228502
6	(alcohol$ or drinking or wine).tw.	876461
7	or/1-6	955932
8	exp Dementia/	451881
9	exp Cognitive Dysfunction/	419113
10	(dementia or cognition or cognitive).tw.	868483
11	or/8-10	1134251
12	(meta-analysis or review).pt.	4706858
13	(systematic$ and (review$ or overview$)).tw.	342078
14	(meta?analy$ or meta analy$).tw.	281997
15	or/12-14	4957423
16	7 and 11 and 15	4677
17	(2017$ or 2018$).dc.[1]	2004172
18	16 and 17	213
19	(2017$ or 2018$).dt.[1]	1353297
20	16 and 19	107
21	18 or 20	320
22	remove duplicates from 21	251

[1] added to EMBASE/MEDLINE in 2017-2018, irrespective of year of publication

Search strategy for primary studies (MEDLINE)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to April 04 2018>

#	Search Statement	Results
1	exp Alcohol drinking/	61992
2	exp Alcohol-Related Disorders/	106648
3	exp Alcoholic Beverages/	17829
4	(alcohol$ or drinking or wine).tw.	367876
5	or/1-4	406690
6	exp Dementia/	144901
7	exp Cognition Disorders/	79912
8	(dementia or cognition or cognitive or neurocognit$ or neuro-cognit$ or alzheimer$).tw.	448982
9	6 or 7 or 8	494437

10	exp Cohort Studies/	1725961
11	Controlled Clinical Trial.pt.	92290
12	exp Case-Control Studies/	905866
13	Risk Factors/	716307
14	(cohort$ or longitudinal or follow-up or "follow up").tw.	1327253
15	(case$ adj3 control$).tw.	143218
16	or/10-15	3104279
17	5 and 9 and 16	3733
18	Animals/ not Humans/	4407379
19	17 not 18	3708
20	limit 19 to yr="2007 -Current"	2252

Search strategy for primary studies (Embase)

Embase Classic+Embase <1947 to 2018 April 06>

#	Search Statement	Results
1	exp drinking behavior/	45554
2	exp alcoholism/	123560
3	exp alcoholic beverage/	28377
4	(alcohol$ or drinking or wine).tw.	519135
5	or/1-4	558699
6	exp dementia/	320588
7	exp cognitive defect/	426609
8	(dementia or cognition or cognitive or neurocognit$ or neuro-cognit$ or alzheimer$).tw.	623351
9	or/6-8	745932
10	exp cohort analysis/	361560
11	exp case control study/	142011
12	exp risk factor/	866500
13	exp longitudinal study/	111824
14	(cohort$ or longitudinal or follow-up or "follow up").tw.	2050163
15	(case$ adj3 control$).tw.	193423
16	or/10-15	2960836
17	5 and 9 and 16	4918
18	exp animal/ not human/	5173603
19	17 not 18	4825
20	limit 19 to yr="2007 -Current"	3659

Search strategy for primary studies (PsycINFO)

PsycINFO <1806 to April Week 1 2018>

#	Search Statement	Results
1	exp alcoholism/	29323
2	exp alcohol drinking patterns/	62837
3	exp drinking behavior/	68306
4	exp binge drinking/	2067
5	exp alcohol abuse/	45823
6	exp alcoholic beverages/	2638
7	(alcohol$ or drinking or wine).tw.	133581
8	or/1-7	136953

9	exp dementia/	69024
10	exp cognitive impairment/	32035
11	(dementia or cognition or cognitive or neurocognit$ or neuro-cognit$ or alzheimer$).tw.	480326
12	or/9-11	484443
13	exp risk factors/	70031
14	exp longitudinal studies/	15920
15	exp followup studies/	12359
16	(cohort$ or longitudinal or follow-up or "follow up").tw.	241129
17	(case$ adj3 control$).tw.	13725
18	or/13-17	314203
19	8 and 12 and 18	1927
20	limit 19 to yr="2007 -Current"	1292

Appendix 2. Data manipulation for each study

Study	Assumptions made in calculating the alcohol consumption (grams(g)/day)	Assumptions made in calculating the statistics used to compute the standardised mean difference
Arntzen 2010	Alcohol measured in glasses. Assumed 13.5g per glass. Alcohol content not specifically noted for Norway, so assumed an average of 12g and 15g (based on [34]). Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Linear regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Adjusted mean differences (and 95%CIs) compared with the referent category (0 to <10g/week) presented. Changed the reference category to non-drinker (current). Calculated pooled standard deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Downer 2015	Alcohol measured in drinks. Assumed 14g per drink. Dose was the reported mean dose within a category.	Linear regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Adjusted mean differences (and 95% CIs) compared with the reference category (current non-drinker) presented. Calculated pooled standard deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Heffernan 2016	Alcohol measured in drinks. Assumed 10g per drink (based on Australian standard). The combined results for males and females were presented, but the alcohol intake within a category (e.g. 'low risk') varied by sex. Therefore, dose was calculated as a weighted average of mid-points for males and females, where the weights reflected the proportion of males and females in the category. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Logistic regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Odds ratios (and 95% CIs) compared with the reference category (current non-drinker) presented. The reciprocal of the OR was computed so that the interpretation of the OR was in the same direction as the other studies (i.e. an OR > 1 means better cognition for exposure categories compared with the referent category). The ORs were converted to SMDs using the method of Chinn 2000. Standard deviations of 1 were assumed for each alcohol level. The variances of the SMDs were recalibrated (by reducing the sample sizes) so that when they were back transformed to the (log) OR scale, they yielded equivalent variances to the observed (log) OR variances.
Horvat 2015	Alcohol measured in grams. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Linear regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Adjusted mean differences (95%CIs) compared with reference category (≥10 g/week and <10 g/day) presented. Changed the reference category to non-drinker (current). Calculated pooled standard

		deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Kesse-Guyot 2012	Alcohol measured in grams. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Analysis of covariance with alcohol modelled as a categorical variable, adjusting for a set of covariates. Adjusted mean differences (95%CIs) compared with reference category (≥ 20 g/day and <30 g/day) presented. Changed the reference category to non-drinker (current). Calculated pooled standard deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Kitamura 2017	Alcohol measured in grams. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Logistic regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Odds ratios (and 95% CIs) compared with the reference category (current non-drinker) presented. The reciprocal of the OR was computed so that the interpretation of the OR was in the same direction as the other studies (i.e. an OR > 1 means better cognition for exposure categories compared with the referent category). The ORs were converted to SMDs using the method of Chinn 2000. Standard deviations of 1 were assumed for each alcohol level. The variances of the SMDs were recalibrated (by reducing the sample sizes) so that when they were back transformed to the (log) OR scale, they yielded equivalent variances to the observed (log) OR variances.
Sabia 2011	Alcohol measured in units. A standard unit is 10g – 12g, so assumed a mean of 11g. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Analysis of covariance with alcohol modelled as a categorical variable, adjusting for a set of covariates. Separate models fitted by education level (primary school, professional qualification, secondary school and more). Adjusted mean differences (95%CIs) compared with reference category (≥ 10 and <20 g/day) presented. Changed the reference category to non-drinker (current). Calculated pooled standard deviations from the confidence limits for each mean difference. Across the strata the mean differences and standard deviations were combined for each level of alcohol consumption. For a particular alcohol level, the mean difference was calculated as a weighted average of the three strata's mean differences, where the weights were the sample sizes. The standard deviations were calculated as the pooled standard deviation of the three standard deviations.

Sabia 2014	Alcohol measured in grams. Dose was the reported median dose within a category, or when not reported, calculated as the mid-point between categories.	Linear mixed model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Adjusted mean differences (95%CIs) compared with reference category (≥10 g/week and <10 g/day) presented. Changed the reference category to non-drinker (current). Calculated pooled standard deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Stott 2008	Alcohol measured in units. Assumed 8g per unit (based on UK standard). Cut-offs in the paper are reported inconsistently. Have assumed the cut-offs outlined in the Statistical Analysis section. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Linear mixed model with alcohol modelled as a categorical variable, adjusting for a set of covariates. No information about how non-drinker was defined, so assumed zero for the dose-response analysis. Calculated pooled standard deviations from the confidence limits for each mean difference. These pooled standard deviations were used in the calculation of the SMD.
Richard 2017	Alcohol measured in drinks. Assumed 12g per drink. The combined results for males and females were presented, but the alcohol intake within a category (e.g. 'moderate') varied by sex and age ((i) men under 65, (ii) men over 65 and women). Assumed the categories for group (ii) since the mean age for each consumption group was approximately 70. Dose calculated as the mid-point between categories. Upper bound of the largest dose category was assigned the lower bound of the largest dose category plus the width of the previous category.	Multinomial logistic regression model with alcohol modelled as a categorical variable, adjusting for a set of covariates. Sample size reduced to account for the fact that the results taken from a subset of the participants included in the multinomial logistic regression model (i.e. the fraction of the cohort that had an outcome of either cognitively healthy longevity or cognitively impaired longevity). The ORs were converted to SMDs using the method of Chinn 2000. Standard deviations of 1 were assumed for each alcohol level. The variances of the SMDs were recalibrated (by reducing the sample sizes) so that when they were back transformed to the (log) OR scale, they yielded equivalent variances to the observed (log) OR variances.

Appendix 3. Changes to protocol

Section	Protocol	Review
Review objectives	We planned to examine the effects of different patterns of alcohol consumption on cognition.	The size and complexity of the review necessitated several changes to scope to ensure review completion within resources and required timeframe. For this reason, we limited our review of studies examining patterns to a summary and synthesis of study characteristics. Risk of bias was not assessed and results were not extracted or reported.
Eligibility criteria	No changes, but some criteria were revised to clarify study eligibility.	Criteria for study design were refined to clarify the definition of prospective alcohol exposure assessment and to explicitly exclude studies that used concomitant measures of alcohol and follow-up cognition in analyses (despite having longitudinal data that would have be suitable for analyses based on prospective alcohol assessment).
Study selection	We planned to have two reviewers independently screen citations and full text.	The large number of studies retrieved for full text screening, together with the complexity of screening, meant that we were unable to independently double screen all studies. A samples of studies was double screened until concordance in screening was achieved. All included studies and any for which screening decision were uncertain were double screened.
Summary and synthesis	We planned to extract, summarise and undertake synthesis of results from studies examining different patterns of consumption.	We extracted and summarised information about the characteristics of studies that examined the effect of different patterns of alcohol consumption, but did not extract or perform any summary or synthesis of results. This was a decision taken to manage the size of the review, based on the large number of studies initially contributing the question about levels of alcohol consumption.
Synthesis	We planned to undertake meta-analyses of pairwise comparisons of different levels of alcohol consumption versus never drinkers or very low level drinkers (zero to <1 g/day).	We did not undertake these analyses since all studies that contributed data suitable for synthesis were able to be included in the dose-response analyses. The dose-response analyses provide a more complete understanding of the relationship between alcohol consumption and the size of the SMDs, since all data are modelled in a single synthesis. Further, from these models, SMDs at any level of alcohol consumption (within the observed range) can be predicted.

Appendix 4. Characteristics of included studies

The following tables provide supplementary information to that reported in the Systematic review report. Table 4.1 summarised the PECO and study design characteristics of studies that examined different patterns of alcohol consumption. Table 4.2 summarises funding sources and potential conflict of interest for studies that examined different levels of alcohol consumption.

Table 4.1. Characteristics of studies that examined the effects of different patterns of alcohol consumption*

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
Boelema 2015 Netherlands Cohort name: Tracking Adolescents' Individual Lives Survey (TRAILS)	Based on 2230 adolescents (50.8% female) aged 10-12 at T0 and 18-20 at final follow-up (T3) Substudy of original large, ongoing cohort	Group assignment according to consumption (average quantity / frequency since last follow-up) at T2 & T3 **Non-drinkers** 'did not consume alcohol' at T2 & T3 **Light-drinkers** < '6 glasses on a weekend day for boys and 5 glasses for girls' at T2 & T3 **Infrequent heavy drinkers** ≥ '6 glasses on a weekend day for boys and 5 glasses for girls' at T2 OR T3 **Increased heavy drinkers ≥ '**6 glasses on a weekend day for boys and 5 glasses for girls' and drinking regularly (last month prevalence ≥ 4 times drinking, i.e., weekly drinking) at T3 **Decreased heavy drinkers** ≥ **'**6 glasses on a weekend day for boys and 5 glasses for girls' and drinking regularly (last month prevalence ≥ 4 times drinking, i.e., weekly drinking) at T2 **Chronic heavy drinkers** ≥ '6 glasses on a weekend day for boys and 5 glasses for girls' and drinking regularly (last month prevalence ≥ 4 times drinking, i.e., weekly drinking) at T2 AND T3 Grams per glass = 10 grams	Observational cohort reporting associations between patterns (quantity / frequency and change in consumption over time) of alcohol consumption and cognitive function among adolescents. Inclusion criteria: children living in 5 municipalities in the North of the Netherlands; born between 1 October 1989 and 30 September 1990 in 2 of the municipalities, and between 1 October 1990 and 30 September 1991 in the other 3. Participants recruited when age 10-12. Exclusion criteria: serious health or language problems. Alcohol ascertainment: Current (quantity, change over time): self-report questionnaire asking about frequency of weekly consumption (how many days do you drink alcohol) and typical intake (how much alcohol (glasses, cans, bottles)). Recall: since last follow-up (2-3 years). Lifetime: measured. Problem drinking: not measured. Cognitive function: Specific cognitive domains (4 outcomes). Four basic executive functions (Amsterdam Neuropsychological Tasks): inhibition, working memory, shift attention, and sustained attention. Change scores calculated by computing z-scores for T0 and T3 measures and subsequently subtracting these scores from each other (T0-T3).	**Study period:** 2001-2010 **Alcohol exposure**: multiple assessments - baseline and then 3 measures at ~ 2-3 year intervals (T0-T3: 2001-2010) (only T2-T3 used in the analysis) **Outcome measures**: baseline and final follow-up (T0 & T3: 2001 & 2010) **Length of outcome follow-up**: ~ 8 years
Carbia 2017 Spain Cohort name: not provided	Based on 155[1] university students (50.1% female) aged 18-19 years at baseline and 24-25 at final follow-up 1. 155 at baseline, 40 at final follow-up.	The classification criteria were based on responses to two questions: the third item of the AUDIT, and one question related to the rate of consumption (drinks per hour). Binge drinking (BD): ≥ 6 drinks per occasion (monthly or weekly) at a rate of ≥3 drinks per hour (heaviest consumption); Non binge drinking (non-BD): < 6	Observational cohort reporting on the relationship between binge drinking trajectory and working memory in Caucasian university students recruited from different faculties of the University of Santiago de Compostela. Inclusion criteria: healthy university students with no other relevant risk factors, such as psychiatric comorbidity or family history of alcoholism. Exclusion criteria: consumption of any other drugs (e.g., opiates, hallucinogens, cocaine, amphetamines, or medically prescribed psychoactive substances),	**Study period**: not reported **Alcohol exposure**: multiple assessments - baseline and then 3 measures at ~ 2 year intervals (T0-T3)

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
	Probably same sample involved in Mota 2013	drinks per occasion (monthly or weekly) at a rate of ≤ 2 drinks per hour (heaviest consumption) Patterns used in the analyses: **Ex-binge drinkers** had abandoned the BD pattern at the 2nd, 3rd, or 4th evaluation **Stable non-binge drinkers** maintained non-binge drinking throughout follow-up **Stable binge drinkers** maintained non-binge drinking throughout follow-up	except nicotine and cannabis; diagnosis of alcohol-use disorders; severe non-corrected motor or sensory deficits; family history of major mental disorder; history of alcoholism in first-and second-degree relatives; history of psychopathology (DSM-IV-TR), such as attention-deficit hyperactivity disorder; conduct disorder or previous diagnosis of depression or anxiety; and current psychopathological symptoms as assessed by the Symptom Checklist-90-R (SCL-90-R). Abstainers were not included in the study. Alcohol ascertainment: The questionnaire included the Alcohol Use Disorders Identification Test (AUDIT) and questions related to alcohol use (rate of consumption, age of onset, etc.). Recall: no information. Lifetime: not measured. Problem drinking: not specifically assessed, but AUDIT (a test for alcohol disorders) used and 'alcohol-use disorder' was an exclusion criteria Cognitive function: specific cognitive domains (1 outcome; 16 measures) Executive function - working memory was assessed using the Self-Ordered Pointing Test, abstract design version (SOPT). The score was categorized into four values ranging from -1 to 1, to deal with negative values.	**Outcome measure**: multiple assessments - baseline and then 3 measures at ~ 2 year intervals (T0-T3) **Length of outcome follow-up**: ~6 years
Carbia 2018 Spain Cohort name: the Compostela Cohort	Based on 63 university students (49.2% female) aged 18 years at baseline (point of first alcohol measure) and 29 years when cognition measured Substudy of original large cohort	**Non-binge drinkers** continuous low alcohol consumption trajectory (AUDIT-C [first three questions] score <4 in all assessments) **Binge drinkers** previous high alcohol consumption trajectory (AUDIT-C [first three questions] score ≥4 at least in three assessments)	Observational cohort examining the relationship between binge drinking and the reflective system (executive functions) in young Caucasian adults recruited from the University of Santiago de Compostela. Inclusion criteria: continuous high alcohol consumption trajectories or continuous low alcohol consumption trajectories at the final follow-up. On the day of testing, the subjects self-reported abstinence from alcohol for at least 48 hr and slept well the night before. Exclusion criteria: severe motor or sensory deficits; history of any neurological or psychiatric disorders; medication that affects cognitive functions; and family history of alcoholism in first degree relatives. Alcohol ascertainment: measured with the AUDIT: AUDIT total scores analysed and AUDIT-C used to classify participants as binge drinkers or non-binge drinkers. Recall: no information. Lifetime: not measured. Problem drinking: AUDIT used: none of the participants scored > 20 (usually considered a cut-off for alcohol dependence). Cognitive function: specific cognitive domains (2 domains, 3 outcomes). Executive function (working memory) was measured with the Self-Ordered Pointing Test (SOPT); cognitive flexibility was measured with the Verbal fluency task and with the Trail Making Test (TMT).Test results appear to be analysed as raw scores.	**Study period**: 2005-2016 **Alcohol exposure**: multiple assessments - baseline and then 5 measures at ~ 2-3 year intervals (T0-T5: 2005-2016) **Outcome measure**: single assessment at final follow-up (T5: 2016) **Length of outcome follow-up**: ~11 years
Gross 2011 United States	Based on 588 medical graduates (8% female) aged 55 years at baseline (point of first	**Frequency** (last year): ≤ 2 times per month (includes those who reported drinking 'rarely), 1-2 times per week, 3-4 times per week, daily or almost daily (referent).	Observational cohort reporting associations between patterns (frequency, change in consumption over time) of alcohol consumption and cognitive function among older adults.	**Study period**: 1986-2005 **Alcohol exposure**: multiple assessments -

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
Cohort name: Johns Hopkins Precursors Study	alcohol measure) and 60-86 years when cognition measured. Substudy of original cohort.	**Change in average consumption** based on average daily intake measured at T0-T5 (recall at each time point: past year) **Problem drinking.** CAGE questionnaire score <2 (referent), score 2+	Inclusion criteria: medical students who graduated from The Johns Hopkins Medical School between 1948 and 1964, and were alive and consented to cognitive testing over the telephone in 2005. Exclusion criteria: none reported Alcohol ascertainment: Current (frequency, change over time): self-report questionnaire asking about frequency of consumption ("daily or almost every day", "3–4×/week", "1–2×/week", "1–2×/month", or "rarely") and typical weekly intake (by type of alcohol; grams of alcohol per drink not reported). Recall: last 12 months. Lifetime: not measured. Problem drinking: CAGE questionnaire. Cognitive function: Global cognitive function (telephone interview for cognitive status (TICS)); specific cognitive domains (4 outcomes). Learning and memory (Hopkins verbal learning test), language (verbal fluency tests, number animals named; number of F, A, and S words), complex attention (Brief Test of Attention). Test results appear to be analysed as raw scores. Higher scores = better cognition.	baseline and then 4 measures at ~ 3-4 year intervals (T0-T5: 1986-2003) **Outcome measures**: single assessment at follow-up (T6: 2005) **Length of outcome follow-up**: ~ 2-19 years (depending on analysis)
Hoang 2014 United States Cohort name: Women Cognitive Impairment Study of Exceptional Aging (WISE)	Based on 1309 community-dwelling women aged ≥65 years at baseline (point of first alcohol measure) and ≥85 years when cognition measured An ancillary study of the Study of Osteoporotic Fractures (SOF)	The study measured average level of consumption per week (see below), but the analysis was based on average change in amount consumed over 16 year period **Average decrease** (referent): between 0 to 0.5 drinks per week **Decrease** average decrease >0.5 drinks per week **Increase** average increase >0 drinks per week Average level of consumption at each measurement point was categorised as: Non-drinker: 0 drinks per week Light: >0 to <3 drinks per week Moderate: ≥ 3 to ≤ 7 drinks per week Heavy: > 7 drinks per week Possible binge drinking: >4 drinks on one occasion.	Observational cohort reporting long-term relationship between changes in alcohol use and cognitive impairment in older community-dwelling American women recruited from population-based listings Inclusion criteria: aged 65 years and older at baseline. Exclusion criteria: a previous diagnosis of dementia at baseline; less than 2 completed visits; no cognitive evaluation; incomplete alcohol use data. Alcohol ascertainment: Current (quantity, change over time): self-report questionnaire asking about the frequency and amount. Recall: past 30 days. Lifetime: not measured. Problem drinking: possible binge drinking. Cognitive function: Clinically significant cognitive impairment (mild cognitive impairment and dementia) (2 outcomes). Outcomes determined using 2 step process. First step: screening process using (1) Modified Mini-Mental State Examination; (2) California Verbal Learning Test delayed recall; (3) Informant Questionnaire on Cognitive Decline in the Elderly; (4) previous dementia diagnosis; or (5) nursing home residence, to identify at risk women. Second step adjudication of cognitive status using panel of clinical experts: diagnosis of dementia was made based on DSM-IV criteria and mild cognitive impairment was diagnosed using a modified Petersen.	**Study period:** 1986-2008 **Alcohol exposure:** multiple assessments - baseline and then at 2-6 year intervals (T0-T4: 1986-2004) **Outcome measures**: baseline and final follow-up (T0 &T5: 1986 & 2008) **Length of outcome follow-up**: 20 years from first alcohol measurement (T0)
Horvat 2015[†] Eastern Europe (Russia, Poland, Czech Republic) Cohort name: HAPIEE (Health,	Based on 28,947 men and women (54.7% female) aged 45-69 years at point of first alcohol measure (T0).	**Frequency** (last year): never, < 1 time per month (referent), 1-3 times per month, 1-4 times per week, ≥ 5 times per week) **Binge drinking** (last year): non-drinker (0 grams per day), non-binger (on one occasion at least monthly: <60 grams for women, <100 grams per	Observational cohort examining associations between different levels and patterns (frequency, binge, problem drinking) of alcohol consumption and cognitive function in older adults. Inclusion criteria: Eligible participants were aged 45-69 years (T0), randomly selected from population registers and electoral lists.	**Study period**: 2002-2008 **Alcohol exposure**: single assessment at baseline (T0: 2002-2005; second

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
Alcohol, and Psychosocial Factors in Eastern Europe) prospective cohort study		day for men; referent), binge drinker (on one occasion at least monthly: ≥60 grams for women, ≥100 grams per day for men). **Problem drinking: n**on-drinker (0 grams per day), CAGE score <2 (referent), score 2+ **Change in average consumption** (average of daily intake T0 and T1, recall 12 months prior): stable non-drinkers (consistently abstained), ex-drinkers (abstained T1 not T0), stable drinkers (stable consumption; referent), reduced drinking (higher consumption T0), increased drinking (higher consumption T1), and those who started drinking (abstained at T0 but not T1).	Exclusion criteria: none reported. Alcohol ascertainment: Current: self-report graduated frequency questionnaire (GFQ) asking about frequency of consumption and number of drinks (by alcohol type; not specified whether asked in relation to a typical occasion/week/other). Recall: last 12 months. Lifetime: not measured. Cognitive function: Specific cognitive domains (4 outcomes). **Learning and memory** (immediate recall of words in 3 x 1 minutes trials; delayed recall of words after other tests administered), **language** (verbal fluency, number animals named in 1 minute), **complex attention** (letter cancelled test for attention, mental speed, concentration). Test results were converted to Z-scores (mean =0; SD = 1) using whole sample means and SDs. Higher scores = better cognition.	assessment made at follow-up, but not used in prospective analysis) **Outcome measures**: baseline and follow-up assessments at ~ 4 year intervals. (T0-T1: 2002-2008) **Length of outcome follow-up**: 4 years from baseline (T0)
Jacobus 2013 United States Cohort name: not reported	Based on 54[2] adolescents (40.7% female) aged 16-19 years at baseline and aged 19–22 years at final follow-up 2. 21 in alcohol + marijuana group	**Controls (CON)** consistent minimal alcohol (and marijuana) use (no binge episodes) since last follow-up **Binge Drinking (BG)** engaging in heavy episodic alcohol use (≥4 drinks on one occasion for females and ≥5 drinks for males) and at least 3 binge episodes since last follow-up **Binge Drinkers with Heavy Marijuana Use (BDHM)** (not relevant to this review)	Observational cohort reporting on prolonged patterns of alcohol (and marijuana use) on white matter integrity and neurocognitive functioning in late adolescents recruited from local high schools. Inclusion criteria: consistent substance use (or non-use) over the 3 year follow-up period (i.e., reported the same pattern of use over 3 years). At project enrolment, binge drinkers were required to have < 10 lifetime marijuana use episodes. Controls were required to have < 20 lifetime alcohol use episodes and binge drinkers were required to have < 150 lifetime alcohol use episodes. Exclusion criteria: history of: a lifetime DSM-IV Axis I disorder (other than cannabis or alcohol abuse or dependence), learning disability, neurological disorder or head trauma with loss of consciousness >2 minutes, serious physical health problem, complicated or premature birth including prenatal substance use; un-correctable sensory impairments; left handedness; MRI contraindications, and use of psychoactive medications (at T0). Alcohol ascertainment: Lifetime and current (quantity/binge, frequency, change): the Customary Drinking and Drug Use Record, and the Timeline Follow-back asking about quantity and frequency. Recall: lifetime and last 28 days. Lifetime: measured. Problem drinking: binge drinking. Cognitive function: **Global cognitive function** (calculated the average 5 domain scores at each time point). Specific cognitive domains: **complex attention, processing speed, verbal memory, visuospatial functioning**, and **executive functioning**. Multiple tests from which a composite score was calculated for each of the 5 domains Each measure was standardized for age and sex, and then converted to z-scores.	**Study period**: not reported **Alcohol exposure**: multiple assessments - baseline and then 2 measures at 1.5 year intervals (T0-T2) **Outcome measures**: multiple assessments - baseline and then 2 measures at 1.5 year intervals (T0-T2) **Length of outcome follow-up**: 3 years
Mota 2013 Spain	Based on 89[3] university students (53.9% female)	The classification criteria were based on responses to two questions: the third item of the AUDIT, and one question related to the rate of	Observational cohort reporting on the relationship between binge drinking trajectory over university years and neuropsychological functioning in university students recruited from the University of Santiago de Compostela.	**Study period**: not reported

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
Cohort name: not provided	aged 18-19 years at baseline and 20-21 at follow-up 3. 143 at baseline; 89 at follow-up and included in the analysis Probably same sample involved in Carbia 2017	consumption (drinks per hour). Binge drinking (BD): ≥ 6 drinks per occasion (monthly or weekly) at a rate of ≥3 drinks per hour (heaviest consumption); Non binge drinking (non-BD): < 6 drinks per occasion (monthly or weekly) at a rate of ≤ 2 drinks per hour (heaviest consumption) Patterns used in the analyses: **Ex-binge drinkers** were classified as binge drinkers at baseline but at follow-up **Non-binge drinkers** did not report a binge drinking pattern at baseline or follow-up **Binge drinkers** reported a binge drinking pattern at baseline and follow-up	Inclusion criteria: healthy university students with no other relevant risk factors, such as psychiatric comorbidity or family history of alcoholism. Participants were required to not take alcohol or any other drug the day of the assessment, and to attend rested and on good health condition. Exclusion criteria: history of neurological disorders (including loss of consciousness > 20 min); history of psychopathology (DSM-IV-TR Axis I and II); current psychopathological symptoms as assessed by the Symptom Checklist-90-R (SCL-90-R). Regular consumption of other drugs (e.g., opiates, hallucinogens, cocaine, amphetamines, or medically prescribed psychoactive substances), except nicotine and cannabis; alcohol-use disorders; severe non-corrected motor or sensory deficits; family history of major mental disorder; history of alcoholism in first-and second-degree relatives. Alcohol ascertainment: The questionnaire included the Alcohol Use Disorders Identification Test (AUDIT) and questions related to alcohol use (rate of consumption, age of onset, etc.). Recall: no information. Lifetime: not measured. Problem drinking: not specifically assessed, but AUDIT (a test for alcohol disorders) used and 'alcohol-use disorder' was an exclusion criteria. . Cognitive function: **specific cognitive domains** (2 outcomes; 18 measures). **Learning and memory** (episodic memory measured using: Rey-Auditory Verbal Learning Test; Logical Memory I and II; Family Pictures I and II). **Executive function** (Digits span backward subtest; the Spatial Location backward subtest of WAIS-III; the Self-Ordered and the Pointing Test (SOPT); Zoo Map and Key Search subtests of the Behavioural Assessment of Dysexecutive Syndrome (BADS)). Test results appear to be analysed as raw scores.	**Alcohol exposure**: baseline and final follow-up (T0 &T1) **Outcome measure**: baseline and final follow-up (T0 &T1) **Length of outcome follow-up**: ~2 years
Ngandu 2007 Finland Cohort name: the Cardiovascular Risk Factors Aging and Dementia (CAIDE) study	Based on 1341[4] (62.3% female) aged 50.2 years (mean) at baseline and aged 65-79 years at follow-up 4. 62 excluded from analysis (missing data) 2 cohorts (baseline dates): 1. 1972/1977 (n = 966) 2. 1982/1987 (n = 313)	1972/1977 cohort **Non-drinker** never drank alcohol **infrequent drinker** drank less frequently than once per month **Frequent drinker** drank once per month or more often 1982/1987 cohort For each alcohol type (beer, wine, spirit) **Non-drinker** did not consume alcohol **Low drinker** consumed amounts in lower half (at the median) **high drinker** consumed amounts in upper half (at the median)	Observational cohort reporting associations between different patterns (frequency, quantity, type) of alcohol consumption in midlife and cognitive function in non-demented elderly persons in Eastern Finland derived from random population-based samples. Inclusion criteria: aged from 65 to 79 years in 1997; non-demented. Exclusion criteria: missing alcohol information. Alcohol ascertainment: (different for each cohort) 1972/1977: current (frequency, change over time): self-report questionnaire, at baseline and follow-up, asking about frequency of consumption (never; < once a month; ≥once month). Change in drinking between midlife and late life was undertaken by creating 9 possible groups, i.e., never drinker in midlife and never drinker in late life etc. Recall: not reported. Lifetime: not measured. Problem drinking: not measured. 1982/1987: Current (quantity): self-report questionnaire, at baseline and follow-up, asking about quantity of beer, wine, and spirits; total weekly alcohol intake (g/ week) was determined, but not reported. 3 categories created (non-drinkers, drinkers divided into two groups at the median). At follow-up	**Study period**: 1972-1998 **Alcohol exposure**: baseline and follow-up (T0 & T1: 1972/1977; 1982/1987 & 1998) **Outcome measure**: single assessment at follow-up (T1: 1998) **Length of outcome follow-up**: 21 years (mean)

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
			questions regarding quantity of cider, and if ceased drinking, were added. Recall: last week. Lifetime: not measured. Problem drinking: not measured. Cognitive function: (for both cohorts) Global cognitive function (MMSE); specific cognitive domains (6 outcomes): episodic memory, semantic memory, subjective memory, prospective memory, executive function, and psychomotor speed. Test results appear to be analysed as raw scores. Higher score = better cognition, except for subjective memory and executive function, where lower score = better cognition.	
Nguyen-Louie 2017 United States Cohort name: not provided	Based on 215[5] adolescents (41% female) aged 12-15 years at baseline and aged ~20 years (mean) at final follow-up 5. 127 in AWDO group Substudy of original large cohort (R01 AA13419)	**Age of first drinking onset (AFDO)** the age of first consuming at least 1 standard drink; analysed as a continuous variable **Age of weekly drinking onset (AWDO)** the age when transitioned into weekly alcohol use; analysed as a continuous variable	Observational cohort examining the influence of age of first drinking onset and age of weekly alcohol use onset on neuropsychological performance in adolescents attending San Diego area public middle schools. Parents were also involved in the study and completed questionnaires. Inclusion criteria: between ages 12 and 15 years at baseline; only participants who consumed at least 1 full drink during follow-up (determined retrospectively). Exclusion criteria: prenatal alcohol (2 or more drinks a given week) or illicit drug exposure; birth prior to 35th gestational week; history of any neurological or DSM-IV Axis I disorder, head trauma or loss of consciousness (>2 minutes), chronic medical illness, learning or intellectual disability, psychoactive medication use; inadequate English comprehension; and non-correctable sensory problems. Potential participants were also excluded if they had ≥10 total lifetime drinking days, ≥3 lifetime experiences with marijuana, ≥5 lifetime cigarette uses, and history of other intoxicant use. All participants were asked not to use alcohol and other recreational drugs for at least 24 hours prior to the study, confirmed with breath alcohol concentration and urine drug screen in the laboratory. Alcohol ascertainment: Age of onset, current (quantity, frequency) were assessed using the Customary Drinking and Drug Use Record and the Timeline Follow-back. Recall: lifetime and last 30 days. Lifetime: measured. Problem drinking: withdrawal symptoms and DSM-IV/DSM-5 SUD criteria were assessed after initiation of use. Cognitive function: Specific cognitive domains (6 outcomes): verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, and visuospatial ability. Various neuropsychological assessments were undertaken which produced 26 variables. These variables were subjected to principal components analysis yielding 6 latent factors/outcomes – as above. Raw scores were transformed into z-scores. All outcomes were further transformed to ensure higher scores = better cognition.	**Study period**: 2003-2016 **Alcohol exposure**: multiple assessments - baseline and then annually **Outcome measures**: multiple assessments - baseline and then annually **Length of outcome follow-up**: 6.8 years (mean)

Study details	Sample	Alcohol exposure categories (patterns)	Details of the included article	Study dates
Richard 2017† United States Cohort name: The Rancho Bernardo Study	Based on 1,334 men and women (54% female) aged 55-84 years at baseline (point of first alcohol measure). Substudy of cohort examining heart disease risk factors.	**Non-drinker (referent)**: 'no past alcohol use' or 'did not drink in last year' **Infrequent drinking**: < 2 times per month **Weekly drinking**: 1-4 times per week **Near daily drinking**: 5-7 times per week	Observational cohort reporting association between different levels and patterns (by frequency) of alcohol consumption and cognitively healthy longevity (survival to age 85). Inclusion criteria: Eligible participants were those with potential to reach 85 years during follow-up period (55-84 years at baseline), and assessed as having intact cognitive function prior to 85th birthday (or an assessment 2 years prior). Exclusion criteria: Missing data on education status. Alcohol ascertainment: Current: self-report questionnaire asking about frequency of consumption and number of drinks (by alcohol type) in a typical week. Item and response options: "how often they consumed alcohol in an average week" (daily/almost daily; 3–4 times/week, 1–2 times/week, 1–2 times/month, or once/month). Lifetime: asked about any 'past alcohol use'. Cognitive function: **Global cognitive function** (MMSE). Raw scores converted to Z-scores (adjusted for sex, age, education) using normative data. Cognitive impairment: Z-scores below −1.5. Outcomes reported: Cognitively Healthy Longevity (CHL: survival to age 85 without cognitive impairment), Cognitively Impaired Longevity (CIL: survival to age 85 with cognitive impairment).	**Study period**: 1984-2009 **Alcohol exposure**: single assessment at baseline (T0: 1984-1987) **Outcome measures**: up to 6 assessments at ~ 4 year intervals. (T1-T6: 1988-2009) **Length of outcome follow-up**: median of 13.9 years from baseline alcohol measurement
Sabia 2011† France Cohort name: GAZEL cohort study	Based on 4,073 men aged ~45-55 years at point of first alcohol measure (T0) and 55-65 years at point of cognition measure (T10). Substudy of GAZEL cohort study which was established to examine various diseases and health-related factors among workers in France's national electricity and gas company.	**Large decrease** (change in alcohol intake over 10 year period): ≥11 drinks fewer per week **Small decrease** (change in alcohol intake over 10 year period): 4 to 10 fewer drinks per week **Stable** (change in alcohol intake over 10 year period): 3 fewer to 4 more drinks per week **Small increase** (change in alcohol intake over 10 year period): 5 to 11 more drinks per week **Large increase** (change in alcohol intake over 10 year period): ≥12 more drinks per week Grams per drink: reported as 10-12 grams	Observational cohort examining association between the trajectory of alcohol consumption (change in consumption over 10 years) and cognition at age ≥55 years. Also examines association between average level of alcohol consumption (based mean of annual measures over time) and cognitive function. Inclusion criteria: Eligible participants were men aged ≥55 years at the time cognition was measured (T10) and working for the electricity and gas company in which the GAZEL cohort was based. Exclusion criteria: Women (due to small number in the GAZEL cohort: ~10%); had no measure of alcohol consumption from T0-T4, T5-T9, or both; did not have full covariate data; did not participate in cognitive tests (n=4525, 48.2%). Alcohol ascertainment: Current: self-report questionnaire asking about frequency of consumption and number of drinks per day (by alcohol type) in last 7 days. Calculated mean change in consumption over 10 year period (based on annual measures of consumption, T0-T9). Lifetime: no information. Cognitive function: Specific cognition domain - **complex attention** measured by the Digit Symbol Substitution Test (DSST; subtest of the Weschler Adult Intelligence Scale). Mean scores reported for number of correct responses on 93 items (score range 0-93; higher score=better cognition).	**Study period**: 1992-2004 **Alcohol exposure**: 10 assessments at ~ 1 year intervals (T0-T9: 1992-2001, or 1993-2002, or 1994-2003; period determined by year of cognitive testing) **Outcome measures**: single assessment (T10: 2002, or 2003, or 2004) **Length of outcome follow-up**: 12 months from baseline (T9)

* For completeness, content is replicated for studies that examined both levels and patterns. Only information pertaining to alcohol categories and ascertainment differs, being limited to either patterns (as reported here) or levels (as reported in the corresponding table).
† Denotes a study that also contributed data on levels of alcohol consumption

Table 4.2. Funding sources, potential conflicts of interest, and ethics approval for studies that examined different levels of alcohol consumption

Study ID	Funding sources	Funders	Review authors' judgment of potential conflicts	Ethics approval
Arntzen 2010	Government Not for profit organisation (including academic)	No information reported in this paper. Various funders identified in Jacobsen 2012 (linked paper), all government or not-for-profit: for example, the National Screening Services, the Research Council of Norway, Northern Norway Regional Health Authority, Norwegian Council on Cardiovascular Diseases and Norwegian Foundation for Health and Rehabilitation	No conflicts identified	Yes
Downer 2015	No direct funding for study	None reported	No conflicts identified	Not reported
Hassing 2018	Government Not for profit organisation (including academic)	The Bank of Sweden Tercentenary Foundation, the Alcohol Research Council of the Swedish Alcohol Retailing Monopoly, National Institute of Aging, National Institutes of Health, and The Swedish Research Council for Health, Working Life and Welfare—Forte	No conflicts identified	Yes
Heffernan 2016	Government	Australian National Health and Medical Research Council	No conflicts identified	Yes
Hogenkamp 2014	Government Not for profit organisation (including academic) Industry (not alcohol)	Swedish Research Council, Åhlens stiftelse, Swedish Brain Research Foundation, Tore Nilsons Foundation, Fredrik och Ingrid Thurings Foundation, Brain Foundation, Åke Wiberg Foundation, and Novo Nordisk Foundation.	No conflicts identified	Yes
Kesse-Guyot 2012	Government Industry	French National Research Agency (nuANR-05-PNRA-010), the French Ministry of Health, Mederic (insurance agency), Sodexo (food catering company), Ipsen (pharmaceutical company), MGEN (insurance agency) and Pierre Fabre (pharmaceutical company).	Author has potentially conflicting interests (some industry funding from a food catering company; authors indicated this is not a conflict). No funder or sponsor involvement in study, but there is some industry funding (food catering company).	Yes
Kitamura 2017	Government Not for profit organisation (including academic)	JSPS KAKENHI Grants, National Cancer Center Research and Development Fund	No conflicts identified	Yes
Lang 2007	Government	National Institutes of Health (NIH), Intramural Research Program, National Institute on Aging, NIH	Insufficient information reported to judge.	Not reported
McGuire 2007	Government	Funder not specified, but the study was conducted by the Centers for Disease Control and Prevention (CDCP), so it is likely CDCP funded the study.	Insufficient information reported to judge.	Not reported
Nooyens 2014	Government Not for profit organisation (including academic)	This subtudy: Internationale Stichting Alzheimer Onderzoek. Main cohort study: Ministry of Public Health, Welfare and Sport of The Netherlands, the National Institute for Public Health and the Environment, Europe Against Cancer programme of the European Commission (early phase). Personal funding: European Commission: Public Health and Consumer Protection Directorate, Ministry of Public Health, Welfare and Sport of The Netherlands.	No conflicts identified	Yes

Study ID	Funding sources	Funders	Review authors' judgment of potential conflicts	Ethics approval
Piumatti 2018	Government Not for profit organisation (including academic)	Economic and Social Research Council, Medical Research Council, Alcohol Research UK	No conflicts identified	Yes
Richard 2017	Government Not for profit organisation (including academic)	National Institute on Alcohol Abuse and Alcoholism, National Institute of Aging, National Institute of Diabetes and Digestive and Kidney Diseases	No conflicts identified	Yes
Sabia 2011	Government Can't tell if all the organisations listed are government.	EDF-GDF and INSERM, the 'Cohortes Santé TGIR Program', Agence nationale de la recherché (ANR) and Agence française de sécurité sanitaire de l'environnement et du travail (AFSSET), and the clinical examinations were funded by the Cnamts.	No conflicts identified	Yes
Sabia 2014	Government Not for profit organisation (including academic)	British Medical Research Council, British Heart Foundation; National Heart, Lung, and Blood Institute, US NIH National Institute on Aging	No conflicts identified	Yes
Samieri 2013a	Government Not for profit organisation (including academic)	National Institutes of Health (NIH), Pôle de Recherche et d'Enseignement Supérieur (PRES) Université de Bordeaux (France)	No conflicts identified	Yes
Solfrizzi 2007	Government Not for profit organisation (including academic)	Italian National Research Council–CNR-Targeted Project on Aging, AFORIGE (Associazione per la Formazione e la Ricerca in Geriatria).	Insufficient information reported to judge.	Not reported
Stott 2008	Not reported	Not reported	No conflicts identified	Yes
Wardzala 2018	Government	VA Merit Review Award, United States Department of Veterans Affairs Biomedical Laboratory Research and Development, National Institutes of Health	No conflicts identified	Yes

Appendix 5. Characteristics of excluded studies – reasons for exclusion

195 studies were excluded from the review based on full-text screening against eligibility criteria.

Of these 195 studies, eight were coded as "near miss" because they met all eligibility criteria but measures of alcohol were collected concomitantly with measures of cognition and the authors modelled the association between alcohol consumption and cognition over time (Table 5.1). In many cases this was done to provide a more reliable measure of alcohol intake over time; however, the approach rendered the studies ineligible because the analysis were not limited to prospective measures of alcohol. For this dataset, it would have been possible to have examined the association between alcohol consumption at a fixed time and future cognition.

A further 19 studies were excluded to narrow the scope of the review to a priority question that could be addressed within the required timeframe and resources. Since a recent systematic (Xu 2017) examined the effects of different levels of alcohol on dementia, and presented a dose response analysis, we excluded 15 studies for which the only eligible outcome was dementia or major cognitive impairment (Table 5.2). In addition, we excluded studies that examined the effects of alcohol among specific subgroups (2 studies: alcohol use disorder or diabetes) or that only examined the effects of high levels of alcohol intake (Table 5.3).

The remaining 176 excluded studies were excluded based on one or more of the pre-specified eligibility criteria, as reported in Tables 5.4-5.12.

Table 5.1 Near miss studies: those that met all criteria, but analysed concomitant measures of alcohol intake and cognition at follow-up (8 studies)

	Reference	Reason for exclusion
1	Beydoun, M. A., A. A. Gamaldo, H. A. Beydoun, T. Tanaka, K. L. Tucker, S. A. Talegawkar, L. Ferrucci and A. B. Zonderman (2014). "Caffeine and ALCOHOL intakes and overall nutrient adequacy are associated with longitudinal cognitive performance among U.S. adults." Journal of Nutrition 144(6): 890-901.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
2	Hagger-Johnson, G., S. Sabia, E. J. Brunner, M. Shipley, M. Bobak, M. Marmot, M. Kivimaki and A. Singh-Manoux (2013). "Combined impact of smoking and heavy ALCOHOL use on cognitive decline in early old age: Whitehall II prospective cohort study." British Journal of Psychiatry 203(2): 120-125.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
3	Jurk, S., E. Mennigen, T. Goschke and M. N. Smolka (2016). "Low-level alcohol consumption during adolescence and its impact on cognitive control development." Addiction Biology: No-Specified.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
4	Klaming, R., J. Annese, D. J. Veltman and H. C. Comijs (2017). "Episodic memory function is affected by lifestyle factors: a 14-year follow-up study in an elderly population." Aging Neuropsychology & Cognition 24(5): 528-542.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
5	Lo, A. H. Y., R. J. Woodman, N. A. Pachana, G. J. Byrne and P. S. Sachdev (2014). "Associations between lifestyle and cognitive function over time in women aged 40-79 years." Journal of Alzheimer's Disease 39(2): 371-383.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
6	Nooyens, A. C. J., H. B. Bueno-de-Mesquita, B. M. van Gelder, M. P. J. van Boxtel and W. M. M. Verschuren (2014). "Consumption of alcoholic beverages and cognitive decline at middle age: the Doetinchem Cohort Study." British Journal of Nutrition 111(4): 715-723.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
7	Samieri, C., O. I. Okereke, E. E Devore and F. Grodstein (2013). "Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women." Journal of Nutrition 143(4): 493-499.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up
8	Zanjani, F., B. G. Downer, T. M. Kruger, S. L. Willis and K. W. Schaie (2013). "ALCOHOL effects on cognitive change in middle-aged and older adults." Aging & Mental Health 17(1): 12-23.	Analysis based on concomitant measures of alcohol and cognition outcomes at follow-up

Table 5.2 Dementia or major cognitive impairment is the only eligible outcome (15 studies; studies in Xu 2017 as indicated)

	Reference	Included in Xu 2017
1	Almeida, O. P., G. J. Hankey, B. B. Yeap, J. Golledge and L. Flicker (2014). "ALCOHOL consumption and cognitive impairment in older men: a mendelian randomization study." Neurology 82(12): 1038-1044.	No - not identified in list of excluded studies
2	Handing, E. P., R. Andel, P. Kadlecova, M. Gatz and N. L. Pedersen (2015). "Midlife Alcohol Consumption and Risk of Dementia Over 43 Years of Follow-Up: A Population-Based Study From the Swedish Twin Registry." Journals of Gerontology Series A-Biological Sciences & Medical Sciences 70(10): 1248-1254.	Yes
3	Heymann, D., Y. Stern, S. Cosentino, O. Tatarina-Nulman, J. N. Dorrejo and Y. Gu (2016). "The Association Between Alcohol Use and the Progression of Alzheimer's Disease." Current Alzheimer Research 13(12): 1356-1362.	No: post-dates search
4	Lobo, E., C. Dufouil, G. Marcos, B. Quetglas, P. Saz, E. Guallar, A. Lobo and Z. Workgroup (2010). "Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline?" American Journal of Epidemiology 172(6): 708-716.	No - not identified in list of excluded studies
5	Mehlig, K., I. Skoog, X. Guo, M. Schutze, D. Gustafson, M. Waern, S. Ostling, C. Bjorkelund and L. Lissner (2008). "Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Goteborg." American Journal of Epidemiology 167(6): 684-691.	Yes
6	Nordstrom, P., A. Nordstrom, M. Eriksson, L. O. Wahlund and Y. Gustafson (2013). "Risk factors in late adolescence for young-onset dementia in men: A nationwide cohort study." JAMA Internal Medicine 173(17): 1612-1618.	No - not identified in list of excluded studies
7	Paganini-Hill, A., C. H. Kawas and M. M. Corrada (2016). "Lifestyle Factors and Dementia in the Oldest-old: The 90+ Study." Alzheimer Disease & Associated Disorders 30(1): 21-26.	Yes
8	Reijs, B. L. R., S. J. B. Vos, H. Soininen, J. Lotjonen, J. Koikkalainen, M. Pikkarainen, A. Hall, R. Vanninen, Y. Liu, S.-K. Herukka, Y. Freund-Levi, G. B. Frisoni, L. Frolich, F. Nobili, M. O. Rikkert, L. Spiru, M. Tsolaki, A. K. Wallin, P. Scheltens, F. Verhey and P. J. Visser (2017). "Association Between Later Life Lifestyle Factors and Alzheimer's Disease Biomarkers in Non-Demented Individuals: A Longitudinal Descriptive Cohort Study." Journal of Alzheimer's Disease 60(4): 1387-1395.	No: post-dates search
9	Stephan, B. C. M., C. Tzourio, S. Auriacombe, H. Amieva, C. Dufouil, A. Alperovitch and T. Kurth (2015). "Usefulness of data from magnetic resonance imaging to improve prediction of dementia: population based cohort study." BMJ 350: h2863.	No - not identified in list of excluded studies
10	Unverzagt, F. W., L. T. Guey, R. N. Jones, M. Marsiske, J. W. King, V. G. Wadley, M. Crowe, G. W. Rebok and S. L. Tennstedt (2012). "ACTIVE cognitive training and rates of incident dementia." Journal of the International Neuropsychological Society 18(4): 669-677.	No - not identified in list of excluded studies
11	Virta, J. J., T. Jarvenpaa, K. Heikkila, M. Perola, M. Koskenvuo, I. Raiha, J. O. Rinne and J. Kaprio (2010). "Midlife alcohol consumption and later risk of cognitive impairment: A twin followup study." Journal of Alzheimer's Disease 22(3): 939-948.	No - not identified in list of excluded studies
12	Weyerer, S., M. Schaufele, B. Wiese, W. Maier, F. Tebarth, H. van den Bussche, M. Pentzek, H. Bickel, M. Luppa, S. G. Riedel-Heller and g. German AgeCoDe Study (2011). "Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 years and older." Age & Ageing 40(4): 456-463.	Yes
13	Xu, G., X. Liu, Q. Yin, W. Zhu, R. Zhang and X. Fan (2009). "Alcohol consumption and transition of mild cognitive impairment to dementia." Psychiatry & Clinical Neurosciences 63(1): 43-49.	No - not identified in list of excluded studies
14	Xue, H., Q. Sun, L. Liu, L. Zhou, R. Liang, R. He and H. Yu (2017). "Risk factors of transition from mild cognitive impairment to Alzheimer's disease and death: A cohort study." Comprehensive Psychiatry 78: 91-97.	No: post-dates search
15	Zhou, S., R. Zhou, T. Zhong, R. Li, J. Tan and H. Zhou (2014). "Association of smoking and ALCOHOL drinking with dementia risk among elderly men in China." Current Alzheimer Research 11(9): 899-907.	Yes

Table 5.3 Study involves a specific subgroup (4 studies)

	Reference	Reason for exclusion
1	Durazzo, T. C., D. L. Pennington, T. P. Schmidt and D. J. Meyerhoff (2014). "Effects of cigarette smoking history on neurocognitive recovery over 8 months of abstinence in ALCOHOL-dependent individuals." Alcoholism: Clinical & Experimental Research 38(11): 2816-2825.	Subgroup: alcohol use disorder or high level consumption
2	Elwood, P., J. Galante, J. Pickering, S. Palmer, A. Bayer, Y. Ben-Shlomo, M. Longley and J. Gallacher (2013). "Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly cohort study." PLoS ONE [Electronic Resource] 8(12): e81877.	Subgroup: alcohol use disorder or high level consumption
3	Miguez-Burbano, M. J., M. Nair, J. E. Lewis and J. Fishman (2009). "The role of alcohol on platelets, thymus and cognitive performance among HIV-infected subjects: are they related?" Platelets 20(4): 260-267.	Subgroup: alcohol use disorder or high level consumption
4	Townsend, M. K., E. Devore, J. H. Kang and F. Grodstein (2009). "The relation between moderate alcohol consumption and cognitive function in older women with type 2 diabetes." Diabetes Research & Clinical Practice 85(3): 322-327.	Subgroup: women with diabetes

The excluded studies that follow (Table 5.4 to 5.12) are listed by the first criterion on which they were excluded. Other reasons for exclusion may apply. An alphabetical list of studies if provided in Appendix 9. Studies coded as clearly irrelevant are listed in the Appendix 9 only.

Table 5.4 Language other than English (2 studies)

	Reference	Reason for exclusion
1	Chanraud, S. and C. Bernard (2015). "Neuroimaging and alcoholism." Annales Medico-Psychologiques 173(3): 249-254.	Language other than English
2	Tang, H. D., Y. H. Yao, R. F. Xu, S. D. Chen and Q. Cheng (2008). "Analysis of cognitive impairment and associated factors of the elderly in Shanghai suburbs." Chinese Journal of Contemporary Neurology and Neurosurgery 8(4): 318-322.	Language other than English

Table 5.5 Does not examine effects of alcohol as an exposure (18 studies)

	Reference	Reason for exclusion
1	Brumback, T., D. Cao, P. McNamara and A. King (2017). "Alcohol-induced performance impairment: a 5-year re-examination study in heavy and light drinkers." Psychopharmacology 234(11): 1749-1759.	Does not examine effects of alcohol as an exposure.
2	Ceccanti, M., D. Hamilton, G. Coriale, V. Carito, L. Aloe, G. Chaldakov, M. Romeo, M. Ceccanti, A. Iannitelli and M. Fiore (2015). "Spatial learning in men undergoing alcohol detoxification." Physiology & Behavior 149: 324-330.	Does not examine effects of alcohol as an exposure.
3	Choi, I.-G., S.-I. Woo, H. J. Kim, D.-J. Kim, B. L. Park, H. S. Cheong, C. F. A. Pasaje, T. J. Park, J. S. Bae, Y. G. Chai and H. D. Shin (2010). "Lack of association between PRNP M129V polymorphism and multiple sclerosis, mild cognitive impairment, alcoholism and schizophrenia in a Korean population." Disease Markers 28(5): 315-321.	Does not examine effects of alcohol as an exposure.
4	Contador, I., F. Bermejo-Pareja, V. Puertas-Martin and J. Benito-Leon (2015). "Childhood and Adulthood Rural Residence Increases the Risk of Dementia: NEDICES Study." Current Alzheimer Research 12(4): 350-357.	Does not examine effects of alcohol as an exposure.
5	Czapla, M., J. J. Simon, B. Richter, M. Kluge, H. C. Friederich, S. Herpertz, K. Mann, S. C. Herpertz and S. Loeber (2015). "The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: Implications for psychotherapeutic treatment." Addiction Biology.	Does not examine effects of alcohol as an exposure.
6	Dingwall, K. M., P. Maruff and S. Cairney (2011). "Similar profile of cognitive impairment and recovery for Aboriginal Australians in treatment for episodic or chronic alcohol use." Addiction 106(8): 1419-1426.	Does not examine effects of alcohol as an exposure.
7	Marceau, E. M., J. Lunn, J. Berry, P. J. Kelly and N. Solowij (2016). "The Montreal Cognitive Assessment (MoCA) is Sensitive to Head Injury and Cognitive Impairment in a Residential Alcohol and Other Drug Therapeutic Community." Journal of Substance Abuse Treatment 66: 30-36.	Does not examine effects of alcohol as an exposure.

	Reference	Reason for exclusion
8	Maurage, F., P. de Timary, J. M. Tecco, S. Lechantre and D. Samson (2015). "Theory of mind difficulties in patients with alcohol dependence: beyond the prefrontal cortex dysfunction hypothesis." Alcoholism: Clinical & Experimental Research 39(6): 980-988.	Does not examine effects of alcohol as an exposure.
9	Nemoto, Y., T. Saito, S. Kanamori, T. Tsuji, K. Shirai, H. Kikuchi, K. Maruo, T. Arao and K. Kondo (2017). "An additive effect of leading role in the organization between social participation and dementia onset among Japanese older adults: the AGES cohort study." BMC Geriatrics 17(1): 297.	Does not examine effects of alcohol as an exposure.
10	Park, K.-Y., H.-S. Hwang, Y.-P. Kim and H.-K. Park (2017). "Risk factors for cognitive decline associated with gait speed in community-dwelling elderly Koreans with MMSE scores of 30." Aging-Clinical & Experimental Research 29(2): 183-189.	Does not examine effects of alcohol as an exposure.
11	Pelletier, S., B. Nalpas, R. Alarcon, H. Rigole and P. Perney (2016). "Investigation of Cognitive Improvement in Alcohol-Dependent Inpatients Using the Montreal Cognitive Assessment (MoCA) Score." Journal of Addiction Print 2016: 1539096.	Does not examine effects of alcohol as an exposure.
12	Pitel, A. L., J. Rivier, H. Beaunieux, F. Vabret, B. Desgranges and F. Eustache (2009). "Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period." Alcoholism: Clinical & Experimental Research 33(3): 490-498.	Does not examine effects of alcohol as an exposure.
13	Quaglino, V., E. De Wever and P. Maurage (2015). "Relations Between Cognitive Abilities, Drinking Characteristics, and Emotional Recognition in Alcohol Dependence: A Preliminary Exploration." Alcoholism: Clinical & Experimental Research 39(10): 2032-2038.	Does not examine effects of alcohol as an exposure.
14	Ritz, L., L. Coulbault, C. Lannuzel, C. Boudehent, S. Segobin, F. Eustache, F. Vabret, A. L. Pitel and H. Beaunieux (2016). "Clinical and Biological Risk Factors for Neuropsychological Impairment in Alcohol Use Disorder." PLoS ONE [Electronic Resource] 11(9): e0159616.	Does not examine effects of alcohol as an exposure.
15	Ros-Cucurull, E., R. F. Palma-Alvarez, C. Cardona-Rubira, E. Garcia-Raboso, C. Jacas, L. Grau-Lopez, A. C. Abad, L. Rodriguez-Cintas, S. Ros-Montalban, M. Casas, J. A. Ramos-Quiroga and C. Roncero (2018). "Alcohol use disorder and cognitive impairment in old age patients: A 6 months follow-up study in an outpatient unit in Barcelona." Psychiatry Research 261: 361-366.	Does not examine effects of alcohol as an exposure.
16	Vachon, D. D., R. F. Krueger, D. E. Irons, W. G. Iacono and M. McGue (2017). "Are Alcohol Trajectories a Useful Way of Identifying At-Risk Youth? A Multiwave Longitudinal-Epidemiologic Study." Journal of the American Academy of Child & Adolescent Psychiatry 56(6): 498-505.	Does not examine effects of alcohol as an exposure.
17	Yamamoto, N., G. Yamanaka, E. Takasugi, M. Ishikawa, T. Yamanaka, S. Murakami, T. Hanafusa, K. Matsubayashi and K. Otsuka (2009). "Lifestyle intervention reversed cognitive function in aged people with diabetes mellitus: two-year follow up." Diabetes Research & Clinical Practice 85(3): 343-346.	Does not examine effects of alcohol as an exposure.
18	Yen, C.-H., Y.-W. Yeh, C.-S. Liang, P.-S. Ho, S.-C. Kuo, C.-C. Huang, C.-Y. Chen, M.-C. Shih, K.-H. Ma, G.-S. Peng, R.-B. Lu and S.-Y. Huang (2015). "Reduced Dopamine Transporter Availability and Neurocognitive Deficits in Male Patients with Alcohol Dependence." PLoS ONE [Electronic Resource] 10(6): e0131017.	Does not examine effects of alcohol as an exposure.

Table 5.6 Examines multiple exposures; **no separate outcome data for alcohol** (N=13)

	Reference	Reason for exclusion
1	Assmann, K. E., C. Lassale, V. A. Andreeva, C. Jeandel, S. Hercberg, P. Galan and E. Kesse-Guyot (2015). "A healthy dietary pattern at midlife, combined with a regulated energy intake, is related to increased odds for healthy aging." Journal of Nutrition 145(9): 2139-2145.	Multiple exposures; does not report separate outcome data for alcohol
2	Bates, M. E., J. F. Buckman, G. T. Voelbel, D. Eddie and J. Freeman (2013). "The mean and the individual: Integrating variable-centered and person-centered analyses of cognitive recovery in patients with substance use disorders." Frontiers in Psychiatry 4.	Multiple exposures; does not report separate outcome data for alcohol
3	Gelber, R. P., H. Petrovitch, K. H. Masaki, R. D. Abbott, G. W. Ross, L. J. Launer and L. R. White (2012). "Lifestyle and the risk of dementia in Japanese-american men." Journal of the American Geriatrics Society 60(1): 118-123.	Multiple exposures; does not report separate outcome data for alcohol

	Reference	Reason for exclusion
4	Kimm, H., P. H. Lee, Y. J. Shin, K. S. Park, J. Jo, Y. Lee, H. C. Kang and S. H. Jee (2011). "Mid-life and late-life vascular risk factors and dementia in Korean men and women." Archives of Gerontology & Geriatrics 52(3): e117-122.	Multiple exposures; does not report separate outcome data for alcohol
5	Latvala, A., A. Tuulio-Henriksson, D. M. Dick, E. Vuoksimaa, J. Suvisaari, R. J. Viken, J. Kaprio and R. J. Rose (2009). "Cognitive functioning and alcohol dependence symptoms in young adulthood: Investigating the association in finnish twins." Behavior Genetics 39(6): 666.	Multiple exposures; does not report separate outcome data for alcohol
6	Lu, D., S. Ren, J. Zhang and D. Sun (2016). "Vascular risk factors aggravate cognitive impairment in first-ever young ischaemic stroke patients." European Journal of Neurology 23(5): 940-947.	Multiple exposures; does not report separate outcome data for alcohol
7	Lyu, J., S. H. Lee and H.-Y. Kim (2016). "Associations between healthy lifestyles and health outcomes among older Koreans." Geriatrics & gerontology international 16(6): 663-669.	Multiple exposures; does not report separate outcome data for alcohol
8	Norton, M. C., J. Dew, H. Smith, E. Fauth, K. W. Piercy, J. C. S. Breitner, J. Tschanz, H. Wengreen, K. Welsh-Bohmer and I. Cache County (2012). "Lifestyle behavior pattern is associated with different levels of risk for incident dementia and Alzheimer's disease: the Cache County study." Journal of the American Geriatrics Society 60(3): 405-412.	Multiple exposures; does not report separate outcome data for alcohol
9	Pearson, K. E., V. G. Wadley, L. A. McClure, J. M. Shikany, F. W. Unverzagt and S. E. Judd (2016). "Dietary patterns are associated with cognitive function in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort." Journal of Nutritional Science 5: e38.	Multiple exposures; does not report separate outcome data for alcohol
10	Sabia, S., A. Singh-Manoux, G. Hagger-Johnson, E. Cambois, E. J. Brunner and M. Kivimaki (2012). "Influence of individual and combined healthy behaviours on successful aging." CMAJ Canadian Medical Association Journal 184(18): 1985-1992.	Multiple exposures; does not report separate outcome data for alcohol
11	Su, P., C.-C. Hsu, H.-C. Lin, W.-S. Huang, T.-L. Yang, W.-T. Hsu, C.-L. Lin, C.-Y. Hsu, K.-H. Chang and Y.-C. Hsu (2017). "Age-related hearing loss and dementia: a 10-year national population-based study." European Archives of Oto-Rhino-Laryngology 274(5): 2327-2334.	Multiple exposures; does not report separate outcome data for alcohol
12	Theadom, A., V. Parag, T. Dowell, K. McPherson, N. Starkey, S. Barker-Collo, K. Jones, S. Ameratunga, V. L. Feigin and B. R. Group (2016). "Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand." British Journal of General Practice 66(642): e16-23.	Multiple exposures; does not report separate outcome data for alcohol
13	Voortman, T., J. C. Kiefte-de Jong, M. A. Ikram, B. H. Stricker, F. J. A. van Rooij, L. Lahousse, H. Tiemeier, G. G. Brusselle, O. H. Franco and J. D. Schoufour (2017). "Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study." European Journal of Epidemiology 32(11): 993-1005.	Multiple exposures; does not report separate outcome data for alcohol

Table 5.7 Alcohol not quantifiable (e.g. qualitative descriptors; alcohol/no alcohol; other) (67 studies)

Of the 67 studies excluded on this criterion, three examined patterns of drinking. These three studies were also ineligible based on other criteria

	Reference	Reason for exclusion
1	Aguirre-Acevedo, D. C., F. Lopera, E. Henao, V. Tirado, C. Munoz, M. Giraldo, S. I. Bangdiwala, E. M. Reiman, P. N. Tariot, J. B. Langbaum, Y. T. Quiroz and F. Jaimes (2016). "Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease: A Retrospective Cohort Study." JAMA Neurology 73(4): 431-438.	Alcohol not quantifiable
2	Barnes, D. E., J. A. Cauley, L.-Y. Lui, H. A. Fink, C. McCulloch, K. L. Stone and K. Yaffe (2007). "Women who maintain optimal cognitive function into old age." Journal of the American Geriatrics Society 55(2): 259-264.	Alcohol not quantifiable
3	Booker, A., L. E. Jacob, M. Rapp, J. Bohlken and K. Kostev (2016). "Risk factors for dementia diagnosis in German primary care practices." International Psychogeriatrics 28(7): 1059-1065.	Alcohol not quantifiable

	Reference	Reason for exclusion
4	Boot, B. P., C. F. Orr, J. E. Ahlskog, T. J. Ferman, R. Roberts, V. S. Pankratz, D. W. Dickson, J. Parisi, J. A. Aakre, Y. E. Geda, D. S. Knopman, R. C. Petersen and B. F. Boeve (2013). "Risk factors for dementia with Lewy bodies: a case-control study." Neurology 81(9): 833-840.	Alcohol not quantifiable
5	Bos, I., S. J. Vos, L. Frolich, J. Kornhuber, J. Wiltfang, W. Maier, O. Peters, E. Ruther, S. Engelborghs, E. Niemantsverdriet, E. E. De Roeck, M. Tsolaki, Y. Freund-Levi, P. Johannsen, R. Vandenberghe, A. Lleo, D. Alcolea, G. B. Frisoni, S. Galluzzi, F. Nobili, S. Morbelli, A. Drzezga, M. Didic, B. N. van Berckel, E. Salmon, C. Bastin, S. Dauby, I. Santana, I. Baldeiras, A. de Mendonca, D. Silva, A. Wallin, A. Nordlund, P. M. Coloma, A. Wientzek, M. Alexander, G. P. Novak, M. F. Gordon, I. Alzheimer's Disease Neuroimaging, A. K. Wallin, H. Hampel, H. Soininen, S.-K. Herukka, P. Scheltens, F. R. Verhey and P. J. Visser (2017). "The frequency and influence of dementia risk factors in prodromal Alzheimer's disease." Neurobiology of Aging 56: 33-40.	Alcohol not quantifiable
6	Brion, M., F. D'Hondt, A.-L. Pitel, B. Lecomte, M. Ferauge, P. de Timary and P. Maurage (2017). "Executive functions in alcohol-dependence: A theoretically grounded and integrative exploration." Drug & Alcohol Dependence 177: 39-47.	Alcohol not quantifiable
7	Ceccanti, M., D. Hamilton, G. Coriale, V. Carito, L. Aloe, G. Chaldakov, M. Romeo, M. Ceccanti, A. Iannitelli and M. Fiore (2015). "Spatial learning in men undergoing alcohol detoxification." Physiology & Behavior 149: 324-330.	Alcohol not quantifiable
8	Chen, L. Y., Y. H. Wu, C. Y. Huang, L. K. Liu, A. C. Hwang, L. N. Peng, M. H. Lin and L. K. Chen (2017). "Predictive factors for dementia and cognitive impairment among residents living in the veterans' retirement communities in Taiwan: Implications for cognitive health promotion activities." Geriatrics and Gerontology International 17(Supplement 1): 7-13.	Alcohol not quantifiable
9	Chen, X., Y. Huang and H. G. Cheng (2012). "Lower intake of vegetables and legumes associated with cognitive decline among illiterate elderly Chinese: a 3-year cohort study." Journal of Nutrition, Health & Aging 16(6): 549-552.	Alcohol not quantifiable
10	Chen, Y., A. R. Sillaire, J. Dallongeville, E. Skrobala, D. Wallon, B. Dubois, D. Hannequin, F. Pasquier and Y. O. D. s. g. Lille (2017). "Low Prevalence and Clinical Effect of Vascular Risk Factors in Early-Onset Alzheimer's Disease." Journal of Alzheimer's Disease 60(3): 1045-1054.	Alcohol not quantifiable
11	Cherbuin, N., C. Reglade-Meslin, R. Kumar, P. Jacomb, S. Easteal, H. Christensen, P. Sachdev and K. J. Anstey (2009). "Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study." Dementia & Geriatric Cognitive Disorders 28(1): 47-55.	Alcohol not quantifiable
12	Chiang, C.-J., P.-K. Yip, S.-C. Wu, C.-S. Lu, C.-W. Liou, H.-C. Liu, C.-K. Liu, C.-H. Chu, C.-S. Hwang, S.-F. Sung, Y.-D. Hsu, C.-C. Chen, S.-I. Liu, S.-H. Yan, C.-S. Fong, S.-F. Chang, S.-L. You and C.-J. Chen (2007). "Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan." American Journal of Geriatric Psychiatry 15(9): 762-771.	Alcohol not quantifiable
13	Fluharty, M. E., J. Heron and M. R. Munafo (2017). "Longitudinal associations of social cognition and substance use in childhood and early adolescence: findings from the Avon Longitudinal Study of Parents and Children." European Child & Adolescent Psychiatry: 20.	Alcohol not quantifiable
14	Fung, A. W. T., G. T. Y. Leung and L. C. W. Lam (2011). "Modulating factors that preserve cognitive function in healthy ageing." East Asian Archives of Psychiatry 21(4): 152-156.	Alcohol not quantifiable
15	Ganguli, M., B. Fu, B. E. Snitz, F. W. Unverzagt, D. A. Loewenstein, T. F. Hughes and C.-C. H. Chang (2014). "Vascular risk factors and cognitive decline in a population sample." Alzheimer Disease & Associated Disorders 28(1): 9-15.	Alcohol not quantifiable
16	Ganguli, M., B. Fu, B. E. Snitz, T. F. Hughes and C.-C. H. Chang (2013). "Mild cognitive impairment: incidence and vascular risk factors in a population-based cohort." Neurology 80(23): 2112-2120.	Alcohol not quantifiable
17	Ganguli, M., C.-W. Lee, B. E. Snitz, T. F. Hughes, E. McDade and C.-C. H. Chang (2015). "Rates and risk factors for progression to incident dementia vary by age in a population cohort." Neurology 84(1): 72-80.	Alcohol not quantifiable

	Reference	Reason for exclusion
18	Gow, A. J., W. Johnson, A. Pattie, M. C. Whiteman, J. Starr and I. J. Deary (2008). "Mental ability in childhood and cognitive aging." Gerontology 54(3): 177-186.	Alcohol not quantifiable
19	Hai, S., B. Dong, Y. Liu and Y. Zou (2012). "Occurrence and risk factors of mild cognitive impairment in the older Chinese population: a 3-year follow-up study." International Journal of Geriatric Psychiatry 27(7): 703-708.	Alcohol not quantifiable
20	Hajek, A. and H.-H. Konig (2016). "Longitudinal Predictors of Functional Impairment in Older Adults in Europe--Evidence from the Survey of Health, Ageing and Retirement in Europe." PLoS ONE [Electronic Resource] 11(1): e0146967.	Alcohol not quantifiable
21	Hao, L., X. Wang, L. Zhang, Y. Xing, Q. Guo, X. Hu, B. Mu, Y. Chen, G. Chen, J. Cao, X. Zhi, J. Liu, X. Li, L. Yang, J. Li, W. Du, Y. Sun, T. Wang, Z. Liu, Z. Liu, X. Zhao, H. Li, Y. Yu, X. Wang, J. Jia and Y. Han (2017). "Prevalence, Risk Factors, and Complaints Screening Tool Exploration of Subjective Cognitive Decline in a Large Cohort of the Chinese Population." Journal of Alzheimer's Disease 60(2): 371-388.	Alcohol not quantifiable
22	Harvanko, A. M., B. L. Odlaug, L. R. N. Schreiber and J. E. Grant (2012). "Cognitive task performance and frequency of ALCOHOL usage in young adults." Journal of Addiction Medicine 6(2): 106-111.	Alcohol not quantifiable
23	Heward, J., L. Stone, S.-M. Paddick, S. Mkenda, W. K. Gray, C. L. Dotchin, J. Kissima, C. Collingwood, B. Swai and R. W. Walker (2018). "A longitudinal study of cognitive decline in rural Tanzania: rates and potentially modifiable risk factors." International Psychogeriatrics: 1-11.	Alcohol not quantifiable
24	Holst, C., J. S. Tolstrup, H. J. Sorensen and U. Becker (2017). "Alcohol dependence and risk of somatic diseases and mortality: a cohort study in 19002 men and women attending alcohol treatment." Addiction 112(8): 1358-1366.	Alcohol not quantifiable
25	Hsu, W.-C., A. C. Tsai, Y.-C. Chen and J.-Y. Wang (2017). "Predicted factors for older Taiwanese to be healthy octogenarians: Results of an 18-year national cohort study." Geriatrics & gerontology international 17(12): 2579-2585.	Alcohol not quantifiable
26	Huang, C.-C., J.-D. Lee, D.-C. Yang, H.-I. Shih, C.-Y. Sun and C.-M. Chang (2017). "Associations Between Geriatric Syndromes and Mortality in Community-Dwelling Elderly: Results of a National Longitudinal Study in Taiwan." Journal of the American Medical Directors Association 18(3): 246-251.	Alcohol not quantifiable
27	Huntley, J., A. Corbett, K. Wesnes, H. Brooker, R. Stenton, A. Hampshire and C. Ballard (2018). "Online assessment of risk factors for dementia and cognitive function in healthy adults." International Journal of Geriatric Psychiatry 33(2): e286-e293.	Alcohol not quantifiable
28	Jacob, L., J. Bohlken and K. Kostev (2017). "Risk Factors for Mild Cognitive Impairment in German Primary Care Practices." Journal of Alzheimer's Disease 56(1): 379-384.	Alcohol not quantifiable
29	Kalapatapu, R. K., K. L. Delucchi, S. Wang, J. D. Harbison, E. E. Nelson and J. H. Kramer (2016). "Substance use history in behavioral-variant frontotemporal dementia versus primary progressive aphasia." Journal of Addictive Diseases 35(1): 36-41.	Alcohol not quantifiable
30	Kim, M. and J.-M. Park (2017). "Factors affecting cognitive function according to gender in community-dwelling elderly individuals." Epidemiology and health 39: e2017054.	Alcohol not quantifiable
31	Kim, S., Y. Kim and S. M. Park (2016). "Association between alcohol drinking behaviour and cognitive function: results from a nationwide longitudinal study of South Korea." BMJ Open 6(4): e010494.	Alcohol not quantifiable
32	Kimura, S., T. Ogata, J. Watanabe, T. Inoue and Y. Tsuboi (2017). "Does cerebral large-artery disease contribute to cognitive impairment?" eNeurologicalSci 8: 5-8.	Alcohol not quantifiable
33	Kitamura, K., Y. Watanabe, K. Nakamura, K. Sanpei, M. Wakasugi, A. Yokoseki, O. Onodera, T. Ikeuchi, R. Kuwano, T. Momotsu, I. Narita and N. Endo (2016). "Modifiable Factors Associated with Cognitive Impairment in	Alcohol not quantifiable

	Reference	Reason for exclusion
	1,143 Japanese Outpatients: The Project in Sado for Total Health (PROST)." Dementia and Geriatric Cognitive Disorders Extra 6(2): 341-349.	
34	Kuzma, E., D. J. Llewellyn, K. M. Langa, R. B. Wallace and I. A. Lang (2014). "History of ALCOHOL use disorders and risk of severe cognitive impairment: a 19-year prospective cohort study." American Journal of Geriatric Psychiatry 22(10): 1047-1054.	Alcohol not quantifiable
35	Lambert, M. E. (2016). "Differences in neurocognitive functioning associated with alcohol consumption in a multiethnic rural cohort: A Project FRONTIER study." Applied Neuropsychology Adult 23(5): 372-378.	Alcohol not quantifiable
36	Langballe, E. M., H. Ask, J. Holmen, E. Stordal, I. Saltvedt, G. Selbaek, A. Fikseaunet, S. Bergh, P. Nafstad and K. Tambs (2015). "Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway." European Journal of Epidemiology 30(9): 1049-1056.	Alcohol not quantifiable
37	Latvala, A., A. E. Castaneda, J. Perala, S. I. Saarni, T. Aalto-Setala, J. Lonnqvist, J. Kaprio, J. Suvisaari and A. Tuulio-Henriksson (2009). "Cognitive functioning in substance abuse and dependence: a population-based study of young adults." Addiction 104(9): 1558-1568.	Alcohol not quantifiable
38	Lee, H., S. Park, K. Lim, K. Lim, Y. Park and J. Jang (2016). "Association between lifestyle and cognitive impairment among women aged 65 years and over in the Republic of Korea." Educational Gerontology 42(3): 198-208.	Alcohol not quantifiable
39	Luck, T., M. Luppa, S. Briel, H. Matschinger, H.-H. Konig, S. Bleich, A. Villringer, M. C. Angermeyer and S. G. Riedel-Heller (2010). "Mild cognitive impairment: incidence and risk factors: results of the leipzig longitudinal study of the aged." Journal of the American Geriatrics Society 58(10): 1903-1910.	Alcohol not quantifiable
40	Lyu, J. and S. H. Lee (2014). "ALCOHOL consumption and cognitive impairment among Korean older adults: does gender matter?" International Psychogeriatrics 26(2): 335-340.	Alcohol not quantifiable
41	McCallum, J., L. A. Simons, J. Simons and Y. Friedlander (2007). "Delaying dementia and nursing home placement: the Dubbo study of elderly Australians over a 14-year follow-up." Annals of the New York Academy of Sciences 1114: 121-129.	Alcohol not quantifiable
42	Nguyen-Louie, T. T., A. N. Simmons, L. M. Squeglia, M. Alejandra Infante, J. P. Schacht and S. F. Tapert (2018). "Earlier alcohol use onset prospectively predicts changes in functional connectivity." Psychopharmacology 235(4): 1041-1054.	Alcohol not quantifiable
43	Nguyen-Louie, T. T., A. Tracas, L. M. Squeglia, G. E. Matt, S. Eberson-Shumate and S. F. Tapert (2016). "Learning and Memory in Adolescent Moderate, Binge, and Extreme-Binge Drinkers." Alcoholism: Clinical & Experimental Research 40(9): 1895-1904.	Alcohol not quantifiable
44	Nguyen-Louie, T. T., N. Castro, G. E. Matt, L. M. Squeglia, T. Brumback and S. F. Tapert (2015). "Effects of Emerging Alcohol and Marijuana Use Behaviors on Adolescents' Neuropsychological Functioning Over Four Years." Journal of Studies on Alcohol & Drugs 76(5): 738-748.	Alcohol not quantifiable
45	Niu, M.-J., F.-Z. Yin, L.-X. Liu, Y. Fang, X.-M. Xuan and G.-F. Wu (2013). "Non-high-density lipoprotein cholesterol and other risk factors of mild cognitive impairment among Chinese type 2 diabetic patients." Journal of Diabetes & its Complications 27(5): 443-446.	Alcohol not quantifiable
46	Nowakowska, K., K. Jablkowska and A. Borkowska (2007). "[Cognitive dysfunctions in patients with alcohol dependence]." Psychiatria Polska 41(5): 693-702.	Alcohol not quantifiable
47	Ormstad, H., T. A. Rosness, A. L. M. Bergem, E. Bjertness and B. H. Strand (2016). "Alcohol consumption in the elderly and risk of dementia related death - A Norwegian prospective study with a 17-year follow-up." International Journal of Neuroscience 126(2): 135-144.	Alcohol not quantifiable
48	Park, B., J. Park, J. K. Jun, K. S. Choi and M. Suh (2013). "Gender differences in the association of smoking and drinking with the development of cognitive impairment." PLoS ONE [Electronic Resource] 8(10): e75095.	Alcohol not quantifiable

	Reference	Reason for exclusion
49	Parrish, K. H., O. E. Atherton, A. Quintana, R. D. Conger and R. W. Robins (2016). "Reciprocal relations between internalizing symptoms and frequency of alcohol use: Findings from a longitudinal study of Mexican-origin youth." Psychology of Addictive Behaviors 30(2): 203-208.	Alcohol not quantifiable
50	Peters, R., N. Beckett, M. Geneva, M. Tzekova, F. H. Lu, R. Poulter, N. Gainsborough, B. Williams, M.-C. de Vernejoul, A. Fletcher and C. Bulpitt (2009). "Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET." Age & Ageing 38(5): 521-527.	Alcohol not quantifiable
51	Schwarzinger, M., B. G. Pollock, O. S. M. Hasan, C. Dufouil, J. Rehm and G. QalyDays Study (2018). "Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective cohort study." The lancet Public Health 3(3): e124-e132.	Alcohol not quantifiable
52	Schwarzinger, M., S. P. Thiebaut, S. Baillot, V. Mallet and J. Rehm (2017). "Alcohol use disorders and associated chronic disease - a national retrospective cohort study from France.[Erratum appears in BMC Public Health. 2017 Sep 22;17 (1):736; PMID: 28938882]." BMC Public Health 18(1): 43.	Alcohol not quantifiable
53	Squeglia, L. M., A. D. Spadoni, M. A. Infante, M. G. Myers and S. F. Tapert (2009). "Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys.[Erratum appears in Psychol Addict Behav. 2010 Mar;24(1):118]." Psychology of Addictive Behaviors 23(4): 715-722.	Alcohol not quantifiable
54	Stephens, C., J. Spicer, C. Budge, B. Stevenson and F. Alpass (2015). "Accounting for differences in cognitive health between older adults in New Zealand and the USA." International Psychogeriatrics 27(4): 591-600.	Alcohol not quantifiable
55	Subramaniam, M., E. Abdin, J. A. Vaingankar and S. A. Chong (2013). "Gender differences in disability in a multiethnic Asian population: the Singapore Mental Health Study." Comprehensive Psychiatry 54(4): 381-387.	Alcohol not quantifiable
56	Takahashi, P. Y., C. R. Caldwell and P. V. Targonski (2011). "Effect of alcohol and tobacco use on vascular dementia: a matched case control study." Vascular Health & Risk Management 7: 685-691.	Alcohol not quantifiable
57	Toda, A., Y. Tagata, T. Nakada, M. Komatsu, N. Shibata and H. Arai (2013). "Changes in Mini-Mental State Examination score in Alzheimer's disease patients after stopping habitual drinking." Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society 13(2): 94-98.	Alcohol not quantifiable
58	Tremolizzo, L., E. Bianchi, E. Susani, E. Pupillo, P. Messina, A. Aliprandi, A. Salmaggi, M. Cosseddu, A. Pilotto, B. Borroni, A. Padovani, C. Bonomini, O. Zanetti, I. Appollonio, E. Beghi and C. Ferrarese (2017). "Voluptuary Habits and Risk of Frontotemporal Dementia: A Case Control Retrospective Study." Journal of Alzheimer's Disease 60(2): 335-340.	Alcohol not quantifiable
59	Vaillant, G. E., O. I. Okereke, K. Mukamal and R. J. Waldinger (2014). "Antecedents of intact cognition and dementia at age 90 years: a prospective study." International Journal of Geriatric Psychiatry 29(12): 1278-1285.	Alcohol not quantifiable
60	van der Heide, I., U. Gehring, G. H. Koppelman and A. H. Wijga (2016). "Health-Related Factors Associated with Discrepancies between Children's Potential and Attained Secondary School Level: A Longitudinal Study." PLoS ONE [Electronic Resource] 11(12): e0168110.	Alcohol not quantifiable
61	Vincze, G., P. Almos, K. Boda, P. Dome, N. Bodi, G. Szlavik, E. Magloczki, M. Pakaski, Z. Janka and J. Kalman (2007). "Risk factors of cognitive decline in residential care in Hungary." International Journal of Geriatric Psychiatry 22(12): 1208-1216.	Alcohol not quantifiable
62	Virag, M., K. Janacsek, A. Horvath, Z. Bujdoso, D. Fabo and D. Nemeth (2015). "Competition between frontal lobe functions and implicit sequence learning: evidence from the long-term effects of alcohol." Experimental Brain Research 233(7): 2081-2089.	Alcohol not quantifiable
63	Vos, S. J. B., M. P. J. van Boxtel, O. J. G. Schiepers, K. Deckers, M. de Vugt, I. Carriere, J.-F. Dartigues, K. Peres, S. Artero, K. Ritchie, L. Galluzzo, E. Scafato, G. B. Frisoni, M. Huisman, H. C. Comijs, S. F. Sacuiu, I. Skoog, K. Irving, C. A. O'Donnell, F. R. J. Verhey, P. J. Visser and S. Kohler (2017). "Modifiable Risk	Alcohol not quantifiable

	Reference	Reason for exclusion
	Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index." Journal of Alzheimer's Disease 58(2): 537-547.	
64	Wadley, V. G., L. A. McClure, V. J. Howard, F. W. Unverzagt, R. C. Go, C. S. Moy, M. R. Crowther, C. R. Gomez and G. Howard (2007). "Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study." Stroke 38(4): 1143-1147.	Alcohol not quantifiable
65	Wang, T., S. Xiao, K. Chen, C. Yang, S. Dong, Y. Cheng, X. Li, J. Wang, M. Zhu, F. Yang, G. Li, N. Su, Y. Liu, J. Dai and M. Zhang (2017). "Prevalence, Incidence, Risk and Protective Factors of Amnestic Mild Cognitive Impairment in the Elderly in Shanghai." Current Alzheimer Research 14(4): 460-466.	Alcohol not quantifiable
66	Weber, E., E. E. Morgan, J. E. Iudicello, K. Blackstone, I. Grant, R. J. Ellis, S. L. Letendre, S. Little, S. Morris, D. M. Smith, D. J. Moore, S. P. Woods and T. Group (2013). "Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection." Journal of Neurovirology 19(1): 65-74.	Alcohol not quantifiable
67	Yen, C.-H., C.-J. Yeh, C.-C. Wang, W.-C. Liao, S.-C. Chen, C.-C. Chen, J. Liang, T.-J. Lai, H.-S. Lin, S.-H. Lee and M.-C. Lee (2010). "Determinants of cognitive impairment over time among the elderly in Taiwan: results of the national longitudinal study." Archives of Gerontology & Geriatrics 50 Suppl 1: S53-57.	Alcohol not quantifiable

Table 5.8 Does not report an eligible outcome. (18 studies: no measure of global cognitive function, domain-specific cognitive function, diagnosis of cognitive impairment)

	Reference	Reason for exclusion
1	Bell, C. L., R. Chen, K. Masaki, P. Yee, Q. He, J. Grove, T. Donlon, J. D. Curb, D. C. Willcox, L. W. Poon and B. J. Willcox (2014). "Late-life factors associated with healthy aging in older men." Journal of the American Geriatrics Society 62(5): 880-888.	Not cognitive function OR diagnosis of cognitive impairment
2	Berntsen, S., J. Kragstrup, V. Siersma, G. Waldemar and F. B. Waldorff (2015). "Alcohol consumption and mortality in patients with mild Alzheimer's disease: a prospective cohort study." BMJ Open 5(12): e007851.	Not cognitive function OR diagnosis of cognitive impairment
3	Britton, A., M. Shipley, A. Singh-Manoux and M. G. Marmot (2008). "Successful aging: the contribution of early-life and midlife risk factors." Journal of the American Geriatrics Society 56(6): 1098-1105.	Cognition part of composite outcome only
4	Cartier, J. L., S. C. Kukreja and E. Barengolts (2017). "LOWER SERUM 25-HYDROXYVITAMIN D IS ASSOCIATED WITH OBESITY BUT NOT COMMON CHRONIC CONDITIONS: AN OBSERVATIONAL STUDY OF AFRICAN AMERICAN AND CAUCASIAN MALE VETERANS." Endocrine Practice 23(3): 271-278.	Cognition part of composite outcome only
5	Ellingson, J. M., K. A. Fleming, A. Verges, B. D. Bartholow and K. J. Sher (2014). "Working memory as a moderator of impulsivity and ALCOHOL involvement: testing the cognitive-motivational theory of ALCOHOL use with prospective and working memory updating data." Addictive Behaviors 39(11): 1622-1631.	Not cognition as an outcome (predictor variable)
6	Feng, Q., J. Son and Y. Zeng (2015). "Prevalence and correlates of successful ageing: a comparative study between China and South Korea." European Journal of Ageing 12(2): 83-94.	Not cognitive function OR diagnosis of cognitive impairment
7	Harper, J., S. M. Malone and W. G. Iacono (2017). "Testing the effects of adolescent alcohol use on adult conflict-related theta dynamics." Clinical Neurophysiology 128(11): 2358-2368.	Not cognitive function OR diagnosis of cognitive impairment
8	Hatchard, T., A. M. Smith, R. E. Halchuk, C. A. Longo, P. A. Fried, M. J. Hogan and I. Cameron (2015). "Effects of low-level alcohol use on cognitive interference: an fMRI study in young adults." Alcohol 49(1): 7-13.	Not cognition as an outcome (predictor variable)
9	Heikkinen, N., E. Niskanen, M. Kononen, T. Tolmunen, V. Kekkonen, P. Kivimaki, H. Tanila, E. Laukkanen and R. Vanninen (2017). "Alcohol	Not cognitive function OR diagnosis of cognitive impairment

	Reference	Reason for exclusion
	consumption during adolescence is associated with reduced grey matter volumes." Addiction 112(4): 604-613.	
10	Langberg, J. M., M. R. Dvorsky, K. L. Kipperman, S. J. Molitor and L. D. Eddy (2015). "Alcohol Use Longitudinally Predicts Adjustment and Impairment in College Students with ADHD: The Role of Executive Functions." Psychology of Addictive Behaviors 29(2): 444-454.	Not cognition as an outcome (predictor variable)
11	Lopez-Caneda, E., F. Cadaveira, A. Crego, A. Gomez-Suarez, M. Corral, M. Parada, F. Caamano-Isorna and S. Rodriguez Holguin (2012). "Hyperactivation of right inferior frontal cortex in young binge drinkers during response inhibition: a follow-up study." Addiction 107(10): 1796-1808.	Not cognitive function OR diagnosis of cognitive impairment
12	Pfefferbaum, A., T. Rohlfing, K. M. Pohl, B. Lane, W. Chu, D. Kwon, B. Nolan Nichols, S. A. Brown, S. F. Tapert, K. Cummins, W. K. Thompson, T. Brumback, M. J. Meloy, T. L. Jernigan, A. Dale, I. M. Colrain, F. C. Baker, D. Prouty, M. D. De Bellis, J. T. Voyvodic, D. B. Clark, B. Luna, T. Chung, B. J. Nagel and E. V. Sullivan (2016). "Adolescent Development of Cortical and White Matter Structure in the NCANDA Sample: Role of Sex, Ethnicity, Puberty, and Alcohol Drinking." Cerebral Cortex 26(10): 4101-4121.	Not cognitive function OR diagnosis of cognitive impairment
13	Postuma, R. B., A. Iranzo, B. Hogl, I. Arnulf, L. Ferini-Strambi, R. Manni, T. Miyamoto, W. Oertel, Y. Dauvilliers, Y.-E. Ju, M. Puligheddu, K. Sonka, A. Pelletier, J. Santamaria, B. Frauscher, S. Leu-Semenescu, M. Zucconi, M. Terzaghi, M. Miyamoto, M. M. Unger, B. Carlander, M.-L. Fantini and J. Y. Montplaisir (2015). "Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study." Annals of Neurology 77(5): 830-839.	Cognition part of composite outcome only
14	Rist, P. M., J. R. Marden, B. D. Capistrant, Q. Wu and M. M. Glymour (2015). "Do physical activity, smoking, drinking, or depression modify transitions from cognitive impairment to functional disability?" Journal of Alzheimer's Disease 44(4): 1171-1180.	Not cognitive function OR diagnosis of cognitive impairment
15	Sawyer, K. S., M. Oscar-Berman, S. Mosher Ruiz, D. A. Galvez, N. Makris, G. J. Harris and E. M. Valera (2016). "Associations Between Cerebellar Subregional Morphometry and Alcoholism History in Men and Women." Alcoholism: Clinical & Experimental Research 40(6): 1262-1272.	Not cognitive function OR diagnosis of cognitive impairment
16	Srinivasa, R. N., H. C. Rossetti, M. K. Gupta, R. N. Rosenberg, M. F. Weiner, R. M. Peshock, R. W. McColl, L. S. Hynan, R. T. Lucarelli and K. S. King (2016). "Cardiovascular Risk Factors Associated with Smaller Brain Volumes in Regions Identified as Early Predictors of Cognitive Decline." Radiology 278(1): 198-204.	Not cognition as an outcome (predictor variable)
17	Sun, Q., M. K. Townsend, O. I. Okereke, E. B. Rimm, F. B. Hu, M. J. Stampfer and F. Grodstein (2011). "Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the nurses' health study." PLoS Medicine / Public Library of Science 8(9): e1001090.	Cognition part of composite outcome only
18	Wang, R., L. Fratiglioni, E. J. Laukka, M. Lovden, G. Kalpouzos, L. Keller, C. Graff, A. Salami, L. Backman and C. Qiu (2015). "Effects of vascular risk factors and APOE epsilon4 on white matter integrity and cognitive decline." Neurology 84(11): 1128-1135.	Not cognition as an outcome (predictor variable)

Table 5.9 Ineligible population (1 study)

	Reference	Reason for exclusion
1	Silverberg, N. D., W. Panenka, G. L. Iverson, J. R. Brubacher, J. R. Shewchuk, M. K. S. Heran, G. C. S. Oh, W. G. Honer and R. T. Lange (2016). "Alcohol Consumption Does not Impede Recovery from Mild to Moderate Traumatic Brain Injury." Journal of the International Neuropsychological Society 22(8): 816-827.	People recovering from a traumatic brain injury

Table 5.10 Clearly not a cohort or nested case control study (e.g. cross sectional, case control, other) (22 studies)

	Reference	Reason for exclusion
1	Au Yeung, S. L., C. Jiang, W. Zhang, T. H. Lam, K. K. Cheng, G. M. Leung and C. M. Schooling (2010). "Moderate alcohol use and cognitive function in the Guangzhou Biobank Cohort study." Annals of Epidemiology 20(12): 873-882.	Not a cohort or nested case control study
2	Banz, B. C. (2015). "An evaluation of executive functions, cognitive control and a neurocognitive profile of college binge." Dissertation Abstracts International: Section B: The Sciences and Engineering 76(1-B(E)): No-Specified.	Not a cohort or nested case control study
3	Braun, A. (2015). "Binge drinking's cognitive and emotional correlates: A multi-definitional investigation." Dissertation Abstracts International: Section B: The Sciences and Engineering 76(1-B(E)): No-Specified.	Not a cohort or nested case control study
4	Buttaro, M. A. (2008). "Vascular risk factors and cognitive functioning in normal elderly." Dissertation Abstracts International: Section B: The Sciences and Engineering 68(8-B): 5600.	Not a cohort or nested case control study
5	Byeon, H., Y. Lee, S. Y. Lee, K. S. Lee, S. Y. Moon, H. Kim, C. H. Hong, S. J. Son and S. H. Choi (2015). "Association of alcohol drinking with verbal and visuospatial memory impairment in older adults: Clinical Research Center for Dementia of South Korea (CREDOS) study." International Psychogeriatrics 27(3): 455-461.	Not a cohort or nested case control study
6	Cairney, S., A. Clough, M. Jaragba and P. Maruff (2007). "Cognitive impairment in Aboriginal people with heavy episodic patterns of alcohol use." Addiction 102(6): 909-915.	Not a cohort or nested case control study
7	Cations, M., B. Draper, L.-F. Low, K. Radford, J. Trollor, H. Brodaty, P. Sachdev, P. Gonski, G. A. Broe and A. Withall (2018). "Non-Genetic Risk Factors for Degenerative and Vascular Young Onset Dementia: Results from the INSPIRED and KGOW Studies." Journal of Alzheimer's Disease 62(4): 1747-1758.	Not a cohort or nested case control study
8	Fama, R., E. V. Sullivan, S. A. Sassoon, A. Pfefferbaum and N. M. Zahr (2016). "Impairments in Component Processes of Executive Function and Episodic Memory in Alcoholism, HIV Infection, and HIV Infection with Alcoholism Comorbidity." Alcoholism: Clinical & Experimental Research 40(12): 2656-2666.	Not a cohort or nested case control study
9	Fan, X., A. O'Donnell, S. P. Singh, R. Pungan and L. C. Perlmuter (2008). "Light to moderate alcohol drinking is associated with higher cognitive function in males with type 2 diabetes." Experimental Aging Research 34(2): 126-137.	Not a cohort or nested case control study
10	Fein, G. and S. McGillivray (2007). "Cognitive performance in long-term abstinent elderly alcoholics." Alcoholism: Clinical & Experimental Research 31(11): 1788-1799.	Not a cohort or nested case control study
11	Franken, I. H. A., M. Luijten, F. M. van der Veen and J. W. van Strien (2017). "Cognitive control in young heavy drinkers: An ERP study." Drug & Alcohol Dependence 175: 77-83.	Not a cohort or nested case control study
12	Garcia, A. M., N. Ramon-Bou and M. Porta (2010). "Isolated and joint effects of tobacco and alcohol consumption on risk of Alzheimer's disease." Journal of Alzheimer's Disease 20(2): 577-586.	Not a cohort or nested case control study
13	Harwood, D. G., A. Kalechstein, W. W. Barker, S. Strauman, P. St George-Hyslop, C. Iglesias, D. Loewenstein and R. Duara (2010). "The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease." International Journal of Geriatric Psychiatry 25(5): 511-518.	Not a cohort or nested case control study
14	Hawkins, L. A., S. Kilian, A. Firek, T. M. Kashner, C. J. Firek and H. Silvet (2012). "Cognitive impairment and medication adherence in outpatients with heart failure." Heart & Lung 41(6): 572-582.	Not a cohort or nested case control study
15	Houston, R. J., J. L. Derrick, K. E. Leonard, M. Testa, B. M. Quigley and A. Kubiak (2014). "Effects of heavy drinking on executive cognitive functioning in a community sample." Addictive Behaviors 39(1): 345-349.	Not a cohort or nested case control study
16	Hurstak, E., J. K. Johnson, L. Tieu, D. Guzman, C. Ponath, C. T. Lee, C. W. Jamora and M. Kushel (2017). "Factors associated with cognitive impairment in a cohort of older homeless adults: Results from the HOPE HOME study." Drug & Alcohol Dependence 178: 562-570.	Not a cohort or nested case control study

	Reference	Reason for exclusion
17	Muller-Oehring, E. M., Y.-C. Jung, A. Pfefferbaum, E. V. Sullivan and T. Schulte (2015). "The Resting Brain of Alcoholics." Cerebral Cortex 25(11): 4155-4168.	Not a cohort or nested case control study
18	Ritchie, S. J., T. C. Bates, J. Corley, G. McNeill, G. Davies, D. C. Liewald, J. M. Starr and I. J. Deary (2014). "ALCOHOL consumption and lifetime change in cognitive ability: a gene x environment interaction study." Age 36(3): 9638.	Not a cohort or nested case control study
19	Smith, K., L. Flicker, A. Dwyer, D. Atkinson, O. P. Almeida, N. T. Lautenschlager and D. LoGiudice (2010). "Factors associated with dementia in Aboriginal Australians." Australian & New Zealand Journal of Psychiatry 44(10): 888-893.	Not a cohort or nested case control study
20	Son, S. J., K. S. Lee, B. H. Oh and C. H. Hong (2012). "The effects of head circumference (HC) and lifetime ALCOHOL consumption (AC) on cognitive function in the elderly." Archives of Gerontology & Geriatrics 54(2): 343-347.	Not a cohort or nested case control study
21	Valls-Serrano, C., A. Verdejo-Garcia and A. Caracuel (2016). "Planning deficits in polysubstance dependent users: Differential associations with severity of drug use and intelligence." Drug & Alcohol Dependence 162: 72-78.	Not a cohort or nested case control study
22	Yamawaki, M., K. Wada-Isoe, M. Yamamoto, S. Nakashita, Y. Uemura, Y. Takahashi, T. Nakayama and K. Nakashima (2015). "Association of cerebral white matter lesions with cognitive function and mood in Japanese elderly people: a population-based study." Brain and Behavior 5(3): e00315.	Not a cohort or nested case control study

Table 5.11 Protocols, reports of baseline data, or studies with less than 6 months follow-up (13 studies)

	Reference	Reason for exclusion
1	(2016). ""Cognitive, emotion control, and motor performance of adolescents in the NCANDA study: Contributions from alcohol consumption, age, sex, ethnicity, and family history of addiction": Correction to Sullivan et al. (2016).[Erratum for Neuropsychology. 2016 May;30(4):449-73; PMID: 26752122]." Neuropsychology 30(7): 829.	Protocol or baseline data only; no eligible paper reporting follow-up data identified
2	Brown, S. A., T. Brumback, K. Tomlinson, K. Cummins, W. K. Thompson, B. J. Nagel, M. D. De Bellis, S. R. Hooper, D. B. Clark, T. Chung, B. P. Hasler, I. M. Colrain, F. C. Baker, D. Prouty, A. Pfefferbaum, E. V. Sullivan, K. M. Pohl, T. Rohlfing, B. N. Nichols, W. Chu and S. F. Tapert (2015). "The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): A Multisite Study of Adolescent Development and Substance Use." Journal of Studies on Alcohol & Drugs 76(6): 895-908.	Protocol or baseline data only; no eligible paper reporting follow-up data identified
3	Corley, J., X. Jia, C. E. Brett, A. J. Gow, J. M. Starr, J. A. M. Kyle, G. McNeill and I. J. Deary (2011). "Alcohol intake and cognitive abilities in old age: the Lothian Birth Cohort 1936 study." Neuropsychology 25(2): 166-175.	< 6 months f/up for all outcome measures
4	Davis, B. J. K., J.-S. Vidal, M. Garcia, T. Aspelund, M. A. van Buchem, M. K. Jonsdottir, S. Sigurdsson, T. B. Harris, V. Gudnason and L. J. Launer (2014). "The ALCOHOL paradox: light-to-moderate ALCOHOL consumption, cognitive function, and brain volume." Journals of Gerontology Series A-Biological Sciences & Medical Sciences 69(12): 1528-1535.	< 6 months f/up for all outcome measures
5	Deckers, K., S. Kohler, M. van Boxtel, F. Verhey, C. Brayne, J. Fleming and C. C. s. collaboration (2017). "Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study." Aging & Mental Health: 1-7.	< 6 months f/up for all outcome measures
6	Dimitrov, I., I. Milanov, N. Deleva and B. Ivanov (2011). "Risk factors for dementia in a community-based sample of the Bulgarian urban population." Archives of the Balkan Medical Union 46(2): 147-149.	< 6 months f/up for all outcome measures
7	Groot, R. H. M., M. L. van Dijk and P. A. Kirschner (2015). "Cohort profile of the GOALS study: A large-scale research of physical activity in Dutch students." British Journal of Educational Technology 46(5): 947-952.	Protocol or baseline data only; no eligible paper reporting follow-up data identified
8	Levy, B., E. Manove and R. D. Weiss (2012). "Recovery of cognitive functioning in patients with co-occurring bipolar disorder and ALCOHOL	< 6 months f/up for all outcome measures

	Reference	Reason for exclusion
	dependence during early remission from an acute mood episode." Annals of Clinical Psychiatry 24(2): 143-154.	
9	Peres, K., F. Matharan, M. Allard, H. Amieva, I. Baldi, P. Barberger-Gateau, V. Bergua, I. Bourdel-Marchasson, C. Delcourt, A. Foubert-Samier, A. Fourrier-Reglat, M. Gaimard, S. Laberon, C. Maubaret, V. Postal, C. Chantal, M. Rainfray, N. Rascle and J.-F. Dartigues (2012). "Health and aging in elderly farmers: the AMI cohort." BMC Public Health 12: 558.	Protocol or baseline data only; no eligible paper reporting follow-up data identified
10	Reas, E. T., G. A. Laughlin, D. Kritz-Silverstein, E. Barrett-Connor and L. K. McEvoy (2016). "Moderate, Regular Alcohol Consumption is Associated with Higher Cognitive Function in Older Community-Dwelling Adults." Jpad 3(2): 105-113.	< 6 months f/up for all outcome measures
11	Roberts, R. O., Y. E. Geda, J. R. Cerhan, D. S. Knopman, R. H. Cha, T. J. H. Christianson, V. S. Pankratz, R. J. Ivnik, B. F. Boeve, H. M. O'Connor and R. C. Petersen (2010). "Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment." Dementia & Geriatric Cognitive Disorders 29(5): 413-423.	< 6 months f/up for all outcome measures
12	Steinberg, S. I., M. D. Sammel, B. T. Harel, A. Schembri, C. Policastro, H. R. Bogner, S. Negash and S. E. Arnold (2015). "Exercise, sedentary pastimes, and cognitive performance in healthy older adults." American Journal of Alzheimer's Disease and Other Dementias 30(3): 290-298.	Protocol or baseline data only; no eligible paper reporting follow-up data identified
13	Sullivan, E. V., T. Brumback, S. F. Tapert, R. Fama, D. Prouty, S. A. Brown, K. Cummins, W. K. Thompson, I. M. Colrain, F. C. Baker, M. D. De Bellis, S. R. Hooper, D. B. Clark, T. Chung, B. J. Nagel, B. N. Nichols, T. Rohlfing, W. Chu, K. M. Pohl and A. Pfefferbaum (2016). "Cognitive, emotion control, and motor performance of adolescents in the NCANDA study: Contributions from alcohol consumption, age, sex, ethnicity, and family history of addiction." Neuropsychology 30(4): 449-473.	Protocol or baseline data only; no eligible paper reporting follow-up data identified

Table 5.12 Other (4 studies)

	Reference	Reason for exclusion
1	Au Yeung, S. L., C. Q. Jiang, K. K. Cheng, B. Liu, W. S. Zhang, T. H. Lam, G. M. Leung and C. M. Schooling (2012). "Evaluation of moderate ALCOHOL use and cognitive function among men using a Mendelian randomization design in the Guangzhou biobank cohort study." American Journal of Epidemiology 175(10): 1021-1028.	Design - Mendelian randomisation
2	Eisenstein, A. R. (2012). "Individual and additive effects of lifestyle behaviors on cognition: A longitudinal study." Dissertation Abstracts International: Section B: The Sciences and Engineering 73(2-B): 914.	Thesis
3	Jones, S. B. (2016). "Association of mid-life alcohol consumption with stroke and cognitive decline in the Atherosclerosis Risk in Communities Study." Dissertation Abstracts International: Section B: The Sciences and Engineering 77(1-B(E)): No-Specified.	Thesis
4	Larsson, S. C., M. Traylor, R. Malik, M. Dichgans, S. Burgess, H. S. Markus and o. b. o. t. I. G. o. A. s. P. CoStream Consortium (2017). "Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis." BMJ 359: j5375.	Design - Mendelian randomisation

Appendix 6. Risk of bias assessment of included studies examining the effects of different levels of alcohol

Arntzen 2010

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Arntzen 2010 Norway Cohort name: the Tromsø Study	Participants were recruited at age 58 years (mean). Those with incomplete alcohol and covariate data were excluded, as were those who reported a stroke.	**Age:** yes*. **Sex**: yes. **SES**: education* (years grouped by primary/part secondary, secondary, high school/A-level, college/university). **Smoking:** yes* (current). **Co-morbidities**: coronary heart disease*, self-report diabetes*, depression*, blood pressure*, BMI*. **Baseline cognition**: no. Other: physical activity*; HDL-cholesterol*	**Measurement**: Self-report data from questionnaire, single assessment at baseline (T0) used in current study. Current: asked "are you a teetotaller", and then "How many times a month do you normally drink alcohol", and "How many glasses of (beer/wine/spirits) do you normally drink in a fortnight" (3 items by type). Participants instructed not to "count low alcohol beer" and to "put 0 if less than once a month". Recall: not reported. Lifetime: no information. **Categories**: No alcohol ("teetotaller"), 4 drinking categories defined (<1, 1-2, 3-4, >5 drinks per fortnight; mean/median intake not reported by group).	No information on who administered the neuropsychological tests. Comparable method of assessment for all participants. No information about whether those who administered the test were aware of alcohol consumption status (blinding), but unlikely that this was the case since alcohol was measured by self-report questionnaire at separate visits.	
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate**. (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious.** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate** (i) Proportions of and reasons for missing participants differ slightly across groups. (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Downer 2015

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis**(noting analysis to account for missing data)
Downer 2015 United States Cohort name: Framingham Heart Study Offspring Cohort	Participants had alcohol measures at age 42 years (mean), and were then invited for baseline cognitive testing age ≥60 (T1). At T1, those with major cognitive impairment, stroke or who did not receive cognitive testing were excluded, as were heavy drinkers (≥ 5 drinks almost daily at T2).	**Age:** yes*. **Sex**: yes*. **SES**: education* (assessed at T1; < high school, high school degree, some college, college degree; WRAT-3* measure of reading/ education quality). **Smoking:** yes* (current, never, former). **Co-morbidities**: no (explicitly stated that did not control for diabetes, hypertension, heart disease, depression). **Baseline cognition**: no. Other: APOE e4 allele status*	**Measurement**: Self-report data from questionnaire, single assessment at baseline (T0; only midlife assessment eligible for SR). Current: asked "how many bottles/glasses/drinks of beer/wine/cocktails" consumed per week (portion size defined for each type). Recall: 12 months. Lifetime: asked "have you ever drunk ≥ 5 drinks almost daily at any time of life" (this group excluded from analysis). **Categories**: Abstainers (0 per week, last 12 months), 3 drinking categories defined (1-6, 7-14, 15-34 drinks per week; mean intake reported by group).	No information on who administered the neurocognitive tests. Appears to be same method of assessment for all participants. No information about whether those who administered the test were aware of alcohol consumption status (blinding), but unlikely that this was the case since alcohol was measured by self-report questionnaire at separate visits.	
Overall risk of bias **Serious** due to confounding, selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Serious** Co-morbidities were not controlled for.	RoB in classification of alcohol consumption: **Serious** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Inclusion of a lifetime measure of heavy drinking may lessen the risk of misclassification of heavy drinkers, but not other past drinkers. Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants are likely to have differed across groups. (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Hassing 2018

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Hassing 2018 Sweden Cohort name: none – data from Swedish Twin Registry	Participants were ~ 56 to 66 years of age at first alcohol measurement (T0). Those with incomplete alcohol or covariate data, a dementia diagnosis at the baseline measure of cognition (T1), and non-drinkers were excluded.	**Age:** yes*. **Sex**: yes*. **SES**: education (years); socioeconomic position* (low, middle, high). **Smoking:** yes* (% ever smoked). **Co-morbidities**: clinical review of medical records: diabetes*, vascular disease* (hypertension, myocardial infarction, heart failure, stroke); BMI*. **Baseline cognition**: yes. All covariates, except BMI, measured ≥20 years from alcohol measurement.	**Measurement**: Self-report data from questionnaire, single assessment at T0 (34 years prior to first cognition measure). Current: Asked whether they drank, how often, and how much on a typical occasion (by type). Items not reported, or whether response categories/portion sizes were defined. Recall: not reported. Lifetime: not measured. **Categories**: Abstainers were excluded. Alcohol consumption analysed as a continuous variable (g/week). No categories, except for descriptive purposes and these were incompletely defined (no upper/lower bound).	No information about who administered cognitive tests (here or in earlier reported referenced for testing methods). Assume same method of assessment for all participants. No information about whether those who administered the test were aware of alcohol consumption status (blinding), but unlikely given the interval between alcohol measurement and cognitive testing.	
Overall risk of bias **Critical** due to missing data and Serious risk of bias due to confounding, selection into the study, and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption (including those excluded due to dementia).	RoB due to confounding: **Serious.** Multiple important domains were measured post-baseline and then adjusted for in the analysis. (ii) No important concerns about timing, reliability and validity, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Misclassification is highly likely (e.g. no measure prior to midlife; and categorisation based on drinking patterns >30 years prior to outcome measurement). RoB due to deviations from exposure as categorised through intervention: **Low** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring the cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Critical.** Very high amount of missing data (61%), not reported if balanced across exposure groups (but unlikely to be balanced), and the analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information.** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Heffernan 2016

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Heffernan 2016 Australia Cohort name: Sydney Memory and Ageing Study	Participants were 70-90 years of age at first alcohol measurement (T0). Those with incomplete alcohol data, MMSE <24 at the baseline measure of cognition (T1), and two or fewer valid scores for cognition measures were excluded.	**Age:** yes*. **Sex**: yes*. **SES**: education* (years). **Smoking:** as part of CVD risk. **Co-morbidities**: CVD risk score* (smoking status, blood pressure, diabetic status, cholesterol/ lipoprotein (or BMI), hypertension medication); depression*. **Baseline cognition**: yes. Other: APO-E allele*.	**Measurement**: Self-report data from interview, single assessment at baseline (T0). Current: asked "how frequently they drank (monthly, weekly, daily)" and "the amount of drinks per drinking session" with pictures of standard drinks by type. Recall: last 12 months. Lifetime: ever "drank more heavily than in the last 12 months"; or if no alcohol in last 12 months "had they ever consumed". **Categories**: No alcohol (last 12 months; referent), 2 drinking categories defined (0-2, >2 drinks per day for women; 0-4, >4 drinks per day for men; mean intake per category reported).	Neuropsychological tests administered by trained research psychologists. Same method of assessment for all participants. No information about whether those who administered the test were aware of alcohol consumption status (blinding), but unlikely that this was the case, especially at the two follow-up assessments where alcohol was not measured.	[complete after result identified]
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption (including those excluded due to cognitive impairment at baseline).	RoB due to confounding: **Moderate**. (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious.** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. categorisation is based on current drinking). Authors reported sensitivity analyses using NIAAA categories (not those based on Australian standards) did not change the results. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate.** (i) Proportions of and reasons for missing participants differ slightly across groups; (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Hogenkamp 2014

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Hogenkamp 2014 Sweden Cohort name: Uppsala Longitudinal Study of Adult Men (ULSAM)	Participants were all men, 70 years of age at first alcohol measurement (T0). Those with incomplete alcohol data were excluded, as were those with an MMSE <25 at the baseline measure of cognition (T0).	**Age:** yes. **Sex**: no (all men). **SES**: education* (primary, secondary, university). **Smoking:** % smokers (yes/no). **Co-morbidities**: history of diabetes*; history of hypertension* (BP or medication); BMI*; CVD risk factors (cholesterol*). **Baseline cognition**: yes. Other: physical activity level*, dietary energy intake*, APO-E allele*.	**Measurement**: Self-report questionnaire, single assessment at baseline (T0). Current: self-report of usual intake of types of alcohol per week, e.g. "How much medium-alcohol beer (number of bottles) do you usually drink per week? Recall: not reported. Lifetime: not measured. Authors report that measure was validated by a 7-day pre-coded dietary record (results not reported). Recall: not reported. Lifetime: not measured. **Categories**: Non-drinkers (0 drinks per week), 3 drinking categories defined (1, 2 and >2 drinks per day, 12 g/drink; mean intake per category reported) and also reported in quintiles. No referent since analysed as continuous variable. Those drinking 0-1.0 g/day were excluded from analysis (n=39).	Neuropsychological tests administered by one of the authors and two trained occupational therapists. Same method of assessment for all participants. No information about whether those administered the test were aware of alcohol consumption status (blinding), but unlikely that this was the case at the follow-up assessment.	Linear regression model of the change between follow-up and baseline TMT-B. Alcohol was modelled as a continuous variable (grams/day). The model adjusted for the covariates: highest educational degree, current smoking, physical activity, total energy intake, BMI, hypertension prevalence, diabetes prevalence, HDL and LDL cholesterol, and APO-E genotype. Results extracted from Table 2. The linear trend coefficient was reported with a p-value. No measure of precision was reported (i.e. confidence interval, standard error).
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption (especially those excluded due to cognitive impairment at baseline).	RoB due to confounding: **Moderate**. (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious**. Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Non/low level drinking group excluded from analysis, lessening issues with misclassification of occasional/former drinkers. However, categorisation based on current drinking. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants are likely to have differed across groups; (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Horvat 2015

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Horvat 2015[†] Eastern Europe Cohort name: HAPIEE (Health, Alcohol, and Psychosocial Factors in Eastern Europe) prospective cohort study	Participants were 45-69 years of age at first alcohol measurement (T0). No exclusion criteria were reported.	**Age:** yes*. **Sex**: yes*. **SES**: education* (primary or less, vocational, secondary, university); household assets index*. **Smoking:** yes* (never, former, current). **Co-morbidities**: self-reported CVD, hypertension, diabetes; high depressive symptoms (measured by CESD-10 scale). **Baseline cognition**: yes (if ≥60 years; 20% sample of those 45-59 years) Other: leisure-time physical activity*.	**Measurement**: Self-report graduated frequency questionnaire, single assessment at baseline (T1 measure not used in prospective analysis). Lifetime: not measured. Current: asked about frequency (6 categories: "never" to "almost every day"), and amount by type of alcohol (beer, wine, spirits; 6 amounts: >10 drinks, 7-9 drinks, 5-6 drinks, 3-4 drinks, 1-2 drinks, 0 drinks). Recall: last 12 months. **Categories**: Non-drinkers (0 drinks in last 12 months), light (referent; women/men: <5/10 grams/day), moderate, heavy (women/men: ≥20/40 g/d). Authors note "baseline information was not available on long-term abstention" so 'non-drinkers' includes lifetime abstainers and former drinkers.	Neuropsychological tests administered by a trained nurse. Same method of assessment for all participants. No information about whether interviewer was aware of alcohol consumption status (blinding), but unlikely that this was the case.	
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious.** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate.** (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking), but low intake was used as referent. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Low**. Data were reasonably complete. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Kesse-Guyot 2012

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Kesse-Guyot 2012 France Cohort name: SU.VI.MAX 2 cohort	Participants were 45-60 years of age at first alcohol measurement (T0). Those with incomplete alcohol data (<3/12 dietary records), covariate data, or incomplete cognitive tests were excluded. Participants were initial selected for a randomised trial of dietary supplements for prevention of cancer and heart disease. Trial eligibility criteria were not reported, but likely that those with pre-existing heart disease were excluded (potentially associated with both alcohol and cognition).	**Age:** yes*. **Sex**: yes. **SES**: education* (primary, secondary, university / equivalent); occupation* (unemployed, manual labour, professional, self-employed/ farmer, managerial). **Smoking:** yes* (never, former, current). **Co-morbidities**: CV events (validated), CVD, measured diabetes*, BMI*, hypertension*, depression* (only at T1, CES-D). **Baseline cognition**: no (asked about 'memory troubles'*) Other: physical activity*.	**Measurement**: Current: 24 hour dietary record (bimonthly over 2 years, randomly assigned across 2 weekend days and 4 week days) asking about the number alcoholic drinks (by type) and portion size (validated photographs of 7 portion sizes, including 2 extreme). Recall: 24 hours. Lifetime: not measured. **Categories**: Non-drinkers. Other categories defined in grams per day (15-29.9 g/day used as referent). Authors note that they may not be able to "distinguish between abstainers and former drinkers" so 'non-drinkers' includes lifetime abstainers and former drinkers.	Neuropsychological tests administered by a trained neuropsychologists. Same method of assessment for all participants. No information about whether interviewer was aware of alcohol consumption status (blinding), but unlikely that this was the case.	
Overall risk of bias **Serious** due to selection bias and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption (especially cardiovascular health).	RoB due to confounding: **Moderate**. i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious**. Multiple assessments to categorise levels of drinking, but short recall for each, which brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Underestimation of intake (by modifying behaviour during measurement period) may amplify problems with misclassification. Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking). RoB due to deviations from exposure as categorised through intervention: **Low**. Unlikely to be any intervention during alcohol measurement that would lead to an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants are likely to have differed across groups; (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information.** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Kitamura 2017

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Kitamura 2017 Japan Cohort name: Murakami Cohort Study	Participants were 44-79 years of age at first alcohol measurement (T0). No exclusion criteria were reported in this paper for this substudy or the original cohort.	Age: yes*. Sex: yes*. SES: education* (junior high, high school, university or above). Smoking: yes (as predictor variable). Co-morbidities: history of stroke*, history of diabetes*, BMI (as predictor variable). Baseline cognition: no. Other: physical activity (as predictor variable).	**Measurement**: Single assessment at baseline (T0). Current: limited information on how alcohol was measured "average frequency, amount, and types of drinks". Recall: 24 hours. Lifetime: no information except that "past drinkers" were initially classified as non-drinkers, suggesting participants may have been asked about lifetime drinking. **Categories**: Non-drinker or rare drinker (<1 gram per week; referent). Other categories defined in grams per week (1-149, 150-299, 300-449, ≥450). "Past drinkers" were included in the same group as other non-drinkers.	No information on who administered the MMSE, or whether they were aware of alcohol consumption status (blinding). Likely to be the same method of assessment for all participants. Since alcohol status was measured at a separate time point, it is likely the assessor was unaware of alcohol status.	
Overall risk of bias **Serious** due to confounding, selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption. Unclear if any health-related study eligibility criteria that may also have led to disproportionate exclusion of sicker drinkers.	RoB due to confounding: **Serious.** At least one known important domain was not controlled for.	RoB in classification of alcohol consumption: **Serious**. Use of a single assessment, and short time frame, to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. unclear if there is a lifetime measure; categorisation based on current drinking). RoB due to deviations from exposure as categorised through intervention: **Low**. Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **No Information**. Unclear if there is any missing data RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Lang 2007

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Lang 2007 United States, United Kingdom Cohort name: English Longitudinal Study of Ageing (ELSA); U.S Health and Retirement Study (HRS)	Participants were ≥65 years of age at first alcohol measurement (T0). No exclusion criteria were reported.	**Age:** yes*. **Sex**: yes* **SES**: education* (years), income*, wealth*. **Smoking:** yes* (never, ex, current). **Co-morbidities**: number of co-morbidities* (0, 1, >2 of heart condition, stroke, hypertension, diabetes, arthritis, dementia), depression*, BMI*. **Baseline cognition**: no. Other: exercise.	**Measurement**: Single assessment at baseline (T0). Lifetime: no information for HRS. For ELSA, non-drinkers asked if "they had quit for health reasons" (reported % never drank, quit for health reasons, quit for other reasons; not separated for analysis and no sensitivity analyses for cognition outcome). Current: asked about frequency ("Do you ever drink alcohol …", if 'yes' "how many days per week") and amount ("on average how much consumed" on drinking days). No information about whether response options for frequency or amount were provided. Recall: last 12 months (ELSA), last 3 months (HRS). **Categories**: 0, >0-1 (referent), >1-2, >2 drinks per day.	No information about how or who administered cognitive tests, although it is likely that the same method of assessment was used for all participants. No information about whether person administering the test was aware of alcohol consumption status (blinding). No information about whether the tests used were valid measures of cognitive function.	Logistic regression model. Alcohol was modelled as a categorical variable. The model was adjusted multi-stage survey sampling and the covariates: age at baseline, sex, BMI, cigarette smoking, comorbidity (heart condition, stroke, high blood pressure, diabetes mellitus, arthritis, or dementia), income, wealth, exercise, depression (HRS data only). Models also fitted separately by sex. Results extracted from Figure 2 and text (pg 4, col 2). OR and CI reported for only one comparison in the text.
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate) Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption. Unclear if any health-related study eligibility criteria that may also have led to disproportionate exclusion of sicker drinkers.	RoB due to confounding: **Moderate.** (i) Confounding expected, all known important confounding domains appropriately controlled for; (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious**. Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking), and not examined for cognition outcome. Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants differ slightly across groups. (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information.** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

McGuire 2007

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
McGuire 2007 United States Cohort name: Second Longitudinal Study of Aging (LSOA II)	Participants were ≥70 years of age at first alcohol measurement (T0). Those with cognitive impairment at baseline (1.5 SD units below the cohort mean), and missing measures of cognitive function were excluded.	**Age:** yes*. **Sex**: yes*. **SES**: education* (years); income (>$20K). **Smoking:** no (but adjusted for covariates associated with smoking). **Co-morbidities**: self-reported number of chronic conditions* (from diabetes, arthritis, heart disease, stroke, cancer, hypertension, asthma) and self-rate health. **Baseline cognition**: yes. Other: marital status*, ethnicity*.	**Measurement**: Self-report, two assessments. Lifetime: no information. Current: asked about frequency ("on how many days in the past year, on average, they drank alcoholic beverages (beer, wine, or liquor)"), and amount ("number of drinks consumed on those days"). No information about whether response options for frequency or amount were provided. Recall: last 12 months. **Categories**: Non-drinkers (referent: 0 drinks in last 12 months), ≤1 drink/day, >1 drink/day. Grams per drink not reported.	Cognitive tests administered in an "adapted" telephone interview; unclear if items are a valid measure. No information on who administered. Appears that the same method of assessment was used for all participants. No information about whether interviewer was aware of alcohol consumption status (blinding), but unlikely that this was the case.	
Overall risk of bias **Critical** due to missing data, also serious risk of bias due to selection into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption (including those excluded due to cognitive impairment).	RoB due to confounding: **Moderate**. i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious**. Use of two assessment (but only 2 years apart) to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low**. Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low.** (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Critical**. Very high amount of missing data (~50%), not reported if balanced across exposure groups (but unlikely to be balanced), and the analysis is unlikely to have addressed bias arising from the missing data. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Piumatti 2018

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Piumatti 2018 United Kingdom Cohort name: UK Biobank prospective cohort	Participants were 40-73 years of age at first alcohol measurement (T0). Those who consumed alcohol infrequently (< one per week), had a history of neurological disorder (e.g. stroke, head trauma), and less than one valid score (from 7) on cognitive tests at baseline were excluded.	**Age:** yes*. **Sex**: yes*. **SES**: education* (no degree, degree); deprivation* (Townsend score). **Smoking:** yes* (non-smoker, previous, current). **Co-morbidities**: BMI*. No other co-morbidities measured or adjusted for. **Baseline cognition**: yes*. Other: physical activity* (walking days/week).	**Measurement**: Self-report questionnaire. Current: asked about frequency ("how often do you drink alcohol?" ['daily or almost daily', '3-4 times a week', 'once or twice a week', '1-3 times a month', 'special occasions only', 'never' 'prefer not to answer']), and amount (those who drank at least once per week asked: "how many alcoholic drinks consumed on average" [by type, volumes provided for standard drink)). Recall: no information. Lifetime: no information. **Categories**: Alcohol consumption treated as a continuous variable in analyses (g/day). Analyses limited to 'weekly drinkers'.	Cognitive tests administered using computer based testing, so objective assessment (no concerns about blinding) The same method of assessment was used for all participants.	Restricted cubic splines of log transformed reaction time (milliseconds). Alcohol was modelled as a continuous variable (log transformed grams/day). A restricted cubic spline places a constraint in the relationship of linearity (between the predictor and outcome) up to a specified amount of alcohol. The model adjusted for the covariates: age, education, sex, and smoking (Table 2, footnote). It is noted that the model also adjusted for baseline cognition, however, the paper provides conflicting information as to whether this occurred (i.e. data presented in Tables 2 and 3 for the same results indicate contrary information re baseline adjustment). Interaction terms included to investigate if the relationship is modified by age and sex. Results extracted from Table 2 (pg 4) and study authors' interpretation (pg 4).
Overall risk of bias **Serious** due to potential for residual confounding, selection of participants into the study and classification alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Serious.** (i) Confounding expected. Most important confounding domains appropriately controlled for, but not diabetes. Some residual confounding possible. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains.	RoB in classification of alcohol consumption: **Serious.** Use of a single assessment to measure levels of drinking brings a risk of error in the measurement of consumption (i.e. variation in drinking patterns over time are missed). Underestimation (through recall) or conscious under-reporting may amplify this problem, as may measuring current intake only (i.e. no measure of lifetime drinking). RoB due to deviations from exposure as categorised through intervention: **Low**. Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Low.** Data were reasonably complete. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Richard 2017

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Richard 2017† United States Cohort name: The Rancho Bernardo Study	Participants were 55-84 years of age at first alcohol measurement (T0). The study outcome was cognitive function (intact or impaired) on or close to 85th birthday. Those who had cognitive impairment at any point prior to their 85th birthday were excluded, as were those unlikely to reach age 85 (at T0).	**Age**: yes*. **Sex**: yes*. **SES**: education (% some college), marital status. **Smoking**: yes* (% never, past, current). **Co-morbidities**: number of co-morbidities* (CVD, diabetes, stroke, TIA, hypertension, liver disease, cancer, metabolic syndrome); depression*, BMI* **Baseline cognition**: no. **Other**: exercise*, waist-hip ratio; self-perceived health compared to peers (better, same, worse), marital status*.	**Measurement**: Self-report questionnaire, single assessment at baseline. Lifetime: asked if "had ever drunk an alcoholic beverage". Current: asked if "had drunk an alcoholic beverage ... within the past 12 months". If 'yes', asked "how often" they "consumed alcohol in an average week" (daily/almost daily; 3–4 times/week, 1–2 times/week, 1–2 times/month, or once/month) and (2) "how many bottles or cans of beer, glasses of wine, mixed drinks, and liqueurs or other drinks they consume during an average week". Recall (current consumption): not stated. **Categories**: Non-drinkers (referent: lifetime abstainers and former drinkers [no drinking last year]), moderate, heavy, excessive. Sensitivity analyses excluding those with self-rated health 'worse than peers' "yielded similar findings".	MMSE administered by a trained interviewer. Same method of assessment for all participants. No information about whether interviewer was aware of alcohol consumption status (blinding), but unlikely that this was the case.	[complete after result identified]
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health (including cognitive impairment) caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate.** (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB due to deviations from exposure as categorised through intervention: **Serious.** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. current and lifetime abstainers included). RoB due to deviations from exposure as categorised: **Low**. Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants differ slightly across intervention groups. (ii) The analysis is unlikely to have addressed the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Sabia 2011

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Sabia 2011 France Cohort name: GAZEL cohort study	Participants were men, ~45-55 years of age at first alcohol measurement (T0), employed by France's national electricity and gas company. Those with <2 alcohol measures (one in each of T0-T4 and T5-T9), missing covariate data, or no cognitive testing were excluded. The authors noted that 'non-drinkers were more likely to participate in the clinical examination, due perhaps to poor health' (p7).	**Age:** yes*. **Sex**: n/a. **SES**: education* (adjusted or stratified by: primary school, professional qualification, secondary school and more), occupational position (adjusted or stratified by: low, intermediate, high). **Smoking:** yes* (current, stopped ≤10years or >10 years ago, never). **Co-morbidities**: blood pressure, cholesterol, BMI (no diabetes or CVD). **Baseline cognition**: no. Other: marital/ cohabitation status*	**Measurement**: 10 annual assessments over 10 years (T0-T9) using a "validated" self-report quantity/ frequency questionnaire, Current: asked "about the frequency and the daily consumption of different alcoholic beverages (wine, beer, aperitif or spirits) … using drawings of standard alcoholic units. Recall: last 7 days. Lifetime: not measured; mean consumption over 10 years calculated from To-T9 data. **Categories**: no alcohol (10 year), four groups for average weekly consumption in units of alcohol (1-3, 4-14 [referent], 15-21, >21).	Same method of assessment for all participants. No information about who administered the neurocognitive tests or whether they were aware of alcohol consumption status (blinding). However, this is a large cohort study and neurocognitive testing was done independently of alcohol measurement, so it is likely the interviewer was unaware of alcohol status.	**Missing data**: Weighted regression was used to account for missing data. Analyses showed similar results.
Overall risk of bias **Serious** due to confounding, selection of participants into the study, classification of alcohol consumption and missing data	RoB in selection of participants into the study: **Serious.** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (declined to participate in alcohol measurement or cognitive testing). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption. Since the study took place in a workplace, this may influence participation in measurement of alcohol intake.	RoB due to confounding: **Serious**. At least one known important domain was not appropriately not controlled for (diabetes; smoking, BMI and other cardiovascular risk factors measured concurrently with cognition).	RoB in classification of alcohol consumption: **Serious**. The use of up to 10 assessments over 10 years to categorise levels of drinking lessens misclassification of consumption (i.e. capturing variation in drinking patterns over time). Contamination of the non-drinking group with occasional/former drinkers may be less likely (e.g. no lifetime measure; but categorisation based last 10 years). However, the workplace setting may result in conscious under-reporting, and participants only required 2 alcohol measures to be eligible, amplifying problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Serious.** Very high amount of missing data (57%), not balanced across exposure groups, but the analysis accounted for the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information**. No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Sabia 2014

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Sabia 2014 England Whitehall II cohort study	Participants were British civil servants, 35-55 years of age at first alcohol measurement (T0). Those with missing alcohol or covariate data, and those who did not participate in the baseline or two follow-up assessments of cognition (T2-T4) were excluded.	**Age:** yes*. **Sex**: yes (stratification variable). **SES**: education* (university degree or higher), occupational position* (high, intermediate, low). **Smoking:** yes* (current, recent or long-term ex, never). **Co-morbidities**: prevalence of diabetes*, CVD*, hypertension*, depression*. **Baseline cognition**: yes. Other: ethnicity*, marital/ cohabitation status* physical activity*, fruit and vegetable consumption*.	**Measurement**: 3 assessments over 10 years (baseline – T0, T1, T2), self-report quantity/ frequency questionnaire. Current: item wording not reported. Recall: last 12 months (any consumption), last 7 days (quantity in 'drinks' by type of alcohol e.g. number of pints). Lifetime: not measured; mean consumption over 10 years calculated from T0, T1, T2 data. **Categories**: abstainers (10 year), cessation (in last 10 years), occasional, and 3 groups for average daily consumption in grams (percentiles: 0-70 [referent], 70-90, >90).	Same method of assessment for all participants. No information about who administered the neurocognitive tests or whether they were aware of alcohol consumption status (blinding). However, this is a large cohort study and it is likely neurocognitive tests were administered independently of other measures and the interviewer was unaware of alcohol status.	Missing data: Linear mixed models were used to estimate the association between alcohol consumption and 10-year cognitive decline, adjusting for covariates that may predict missing data.
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate**. (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding. The authors cautioned about interpretation of results for abstainers (10 year), noting they were likely to have different characteristics (e.g. higher proportion of women who weren't white compared to other groups).	RoB in classification of alcohol consumption: **Serious.** The use of up to 3 assessments over 10 years to categorise levels of drinking lessens misclassification of consumption (i.e. variation in drinking patterns over time are more likely to be captured). Contamination of the non-drinking group with occasional/former drinkers may be less likely (e.g. no lifetime measure; but categorisation based last 10 years). However, the workplace setting may result in conscious under-reporting, amplifying problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate.** (i) Proportions of and reasons for missing participants differ slightly across intervention groups; (ii) The analysis provides unbiased estimates under the assumption that the data are missing at random. RoB in selection of the reported result: **No Information.** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Samieri 2013

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Samieri 2013 United States Women's Health Study	Participants were women, ≥60 years of age at first alcohol measurement (T0). Those with missing dietary data were excluded ('dietary data' not defined, but assumed to include alcohol). Participants were initially recruited for a trial of aspirin and vitamin E for prevention of CVD and cancer. Trial eligibility criteria were not reported, but likely that those with pre-existing heart disease were excluded (potentially associated with both alcohol and cognition).	**Age:** yes*. **Sex**: n/a. **SES**: education* (bachelor's degree or higher), household income* (≥$50K/year). **Smoking:** yes* (current). **Co-morbidities**: history of diabetes*, hypertension*, hypercholesterolemia*, depression* (at baseline cognitive test), BMI*. **Baseline cognition**: yes. Other: physical activity*, diet*, energy intake*, ethnicity*, hormone use*.	**Measurement**: Current: single assessment (T0) using self-report food frequency questionnaire asking about frequency of consumption of foods and beverages, including alcohol ("never or less than once a month" to "six times per day"), and portion size (standard portion sizes were specified). Recall period: last 12 months. Lifetime: no information. **Categories**: non-drinkers (0 last 12 months, referent), 1-14.9 g/day, ≥15 g/day. Possible that non-drinker category includes former drinkers and abstainers.	Telephone interview administered by a trained nurse (tool validated for telephone administration). Same method of assessment for all participants, but no information about whether interviewer was aware of alcohol consumption status (blinding). However, alcohol measures collected >5 years prior so it is likely the interviewer was unaware of alcohol status.	Linear regression model of the average of three measures of global cognitive function. Alcohol was modelled as a categorical variable. The model adjusted for the covariates: Models were adjusted for age at the start of cognitive testing, race, higher education, annual household income, energy intake, Women's Health Study randomized treatment assignment, regular vigorous exercise, body mass index, current smoking, history of type 2 diabetes, history of hypertension, history of hypercholesterolemia, post-menopausal hormone use, and history of depression. Results extracted from Table 2. No information on the scale range or standard deviation of the global cognitive function outcome (which is a linear combination of z-scores) is provided, precluding clinical interpretation.
Overall risk of bias **Serious** due to selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate). Potential to bias through exclusion of drinkers with poorer health caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate**. (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious**. Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low**. (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Moderate**. (i) Proportions of and reasons for missing participants differ slightly across intervention groups. (ii) The analysis is unlikely to have accounted for the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Solfrizzi 2007

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Solfrizzi 2007 Italy Cohort name: Italian Longitudinal Study on Aging (ILSA)	Participants were 65-84 years of age at first alcohol measurement (T0). Those with a confirmed diagnosis of dementia at baseline assessment of cognition (T0), with unknown level of education, or who refused cognitive testing were excluded.	**Age:** yes*. **Sex**: yes*. **SES**: education* (years). **Smoking:** yes* (cigarette pack-years). **Co-morbidities**: coronary artery disease* (CAD), stroke*, diabetes, hypertension*, (all confirmed through clinical exam), total cholesterol*, (BMI/obesity not mentioned). **Baseline cognition**: yes. Other: medications* (anxiolytics).	**Measurement**: Current: single assessment (T0) using self-report food frequency questionnaire asking about frequency of consumption of foods and beverages, including alcohol (times per day/month/year), and portion size (number of drinks by alcohol type; 3 portions sizes). Recall: last 12 months. Lifetime: asked 'when they had begun to drink' and 'how much beer or wine per day ever since' (to identify former drinkers, and changed patterns). **Categories**: non-drinkers (0 last 12 months, referent). Drinking groups: >1, 1-2, ≥2 drinks/day (15 grams alcohol per drink). Sensitivity analyses removing former drinkers from abstainer group did not alter results	Clinical evaluation by a trained neurologist. It is not reported whether the neurologist was aware of the participants alcohol status (blinding). However the clinical exam and collection of alcohol data occurred >3 years apart, so it is unlikely the neurologist was aware of alcohol consumption status.	
Overall risk of bias **Serious** due to selection of participants into the study, classification of alcohol consumption and missing data	RoB in selection of participants into the study: **Serious** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health (including cognitive impairment) caused or exacerbated by alcohol consumption.	RoB due to confounding: **Moderate** (i) Confounding expected. All known important confounding domains appropriately controlled for. (ii) No important concerns about the timing, or validity and reliability, of measurement of confounding domains, such that we do not expect serious residual confounding.	RoB in classification of alcohol consumption: **Serious** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking), but the authors reported that sensitivity analysis removing former drinkers did not alter results. RoB due to deviations from exposure as categorised through intervention: **Low** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Serious** (i) Proportions of missing participants differ substantially across interventions; or reasons for missing data differ substantially across groups; and (ii) The analysis is unlikely to have accounted for the risk of bias arising from the missing data. RoB in selection of the reported result: **No Information** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Stott 2007

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Stott 2007 United Kingdom, Netherlands Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)	Participants were 70-82 years of age at first alcohol measurement (T0). Those with an MMSE≤24 at baseline assessment of cognition (T0), or a history of drug or alcohol abuse were excluded.	**Age:** yes*. **Sex**: yes. **SES**: education* (years). **Smoking:** yes* (current). **Co-morbidities**: prevalence of diabetes, history of vascular disease*, incident stroke*, blood pressure, BMI*. **Baseline cognition**: yes* (MMSE). Other: country* (Scotland, Ireland, Netherlands), body weight*.	**Measurement**: Single assessment (baseline – T0). No information about tools/items used. Current: item wording not reported "units per week". Recall: last month. Lifetime: no information. **Categories**: non-drinker (not defined; referent), low and moderate intake for average daily consumption.	Same method of assessment for all participants. Trained nurses administered the neurocognitive tests. No information about whether they were aware of alcohol consumption status (blinding). However, cognitive data were collected as trial outcomes, at 12, 24, 36 months after baseline, so it is likely the interviewer was unaware of alcohol status.	
Overall risk of bias **Serious** due to confounding, selection of participants into the study and classification of alcohol consumption	RoB in selection of participants into the study: **Serious**. The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health (including cognitive impairment) caused or exacerbated by alcohol consumption.	RoB due to confounding: **Serious**. At least one known important domain was not appropriately measured, or not controlled for (diabetes)	RoB in classification of alcohol consumption: **Serious**. Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. no lifetime measure; categorisation based on current drinking). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low.** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Low.** No missing data, all participants included in the analysis RoB in selection of the reported result: **No Information.** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Wardzala 2018

Study ID **Country**	**Sample**	**Confounders measured (*adjusted for)**	**Ascertainment of alcohol consumption**	**Ascertainment of cognitive function outcome**	**Data & analysis** (noting analysis to account for missing data)
Wardzala 2018 United States Cohort name: Oregon Brain Aging Study (OBAS); Intelligent Systems for Assessing Aging Changes (ISAAC) study	Participants were ~80 years of age or older at first alcohol measurement (T0). Those with cognitive impairment (MMSE≤24, CDR of >0.5) at baseline assessment of cognition (T0), or missing alcohol or outcome data were excluded.	**Age:** yes*. **Sex**: yes. **SES**: education* (years). **Smoking:** no. **Co-morbidities**: Cumulative Illness Rating Scale* (CIRS; measures co-morbidities and includes cardiovascular disease but as part of an overall score among other conditions), diabetes, hypertension, BMI. **Baseline cognition**: yes. Other: ApoE4 genotype*, Caucasian*.	**Measurement**: Single assessment at T0. Self-report questions administered at interview. Current: If "ever consumed >1 drink/week for >3 months", then asked about frequency ("average days per week" (1-2, 3-5, daily)), and amount ("average quantity in drinks per day" (1, 2-3, ≥4)), and how often they drank ≥4 per occasion. Lifetime: Quantity/ frequency questions asked for age '40-current', '19-39' and '0-18' years. Past drinkers: asked age when they quit. Recall: current to 80 years. **Categories**: Rare/never (0 drinks/week for any 3 month period over lifetime), 2 drinking categories (<3 / <4 drinks/day for men/women; ≥3 / ≥4 drinks/day for men/women). Grams per drink not reported.	Cognitive tests administered in face-to-face interview by research personnel (Kaye 2011). The same method of assessment was used for all participants. No information about whether interviewer was aware of alcohol consumption status (blinding), but alcohol and cognitive measures seem to have been taken place at the same time.	Regression model of annual rates of change. The rates of change were taken from a linear mixed model that modelled log MMSE with subject-specific random effects and fixed effects rates. Alcohol was modelled as a categorical variable. The set of covariates adjusted for is not clear, but likely to have been: age, education, the Cumulative Illness Rating Scale, and expression of the apolipoprotein E, isoform 4 (ApoE 4) genotype. An interaction was included between sex and alcohol consumption categories. Results extracted from Figure 2 (B).
Overall risk of bias **Serious** due to confounding, selection of participants into the study, and classification of alcohol consumption	RoB in selection of participants into the study: **Serious.** The lag time between initiating drinking and enrolment to the study means that those who previously experienced harmful outcomes associated with drinking may be excluded (because they died or were inaccessible, declined or were unable to participate, or did not meet health-related study eligibility criteria). Potential to bias through exclusion of drinkers with poorer health (including cognitive impairment) caused or exacerbated by alcohol consumption.	RoB due to confounding: **Serious.** At least one known important domain (smoking) was not appropriately not controlled for. Co-morbidities were considered to be adjusted for based on adjustments for the CIRS.	RoB in classification of alcohol consumption: **Serious.** Use of a single assessment to categorise levels of drinking brings a risk of misclassifying consumption (i.e. variation in drinking patterns over time are missed). Contamination of the non-drinking group with occasional/former drinkers is likely (e.g. lifetime measure based on long-term recall at age 80). Underestimation (through recall) or conscious under-reporting may amplify problems with misclassification. RoB due to deviations from exposure as categorised through intervention: **Low** Although plausible, intervention during alcohol measurement (e.g.an interviewer noting high alcohol intake), is unlikely to have an important effect on behaviour.	RoB in measurement of outcomes: **Low** (i) The methods of outcome assessment were comparable across alcohol consumption groups. (ii) The outcome assessors were likely to be unaware of alcohol consumption status of study participants. (iii) Any error in measuring cognition is likely to be unrelated to alcohol consumption status.	RoB due to missing outcome data: **Low**. Data were reasonably complete RoB in selection of the reported result: **No Information** No protocol (or statistical analysis plan) identified from which to determine if measures or analyses reported were selected on the basis of results. Hence there is too little information to make a judgement.

Appendix 7. Results from sensitivity analyses

Females

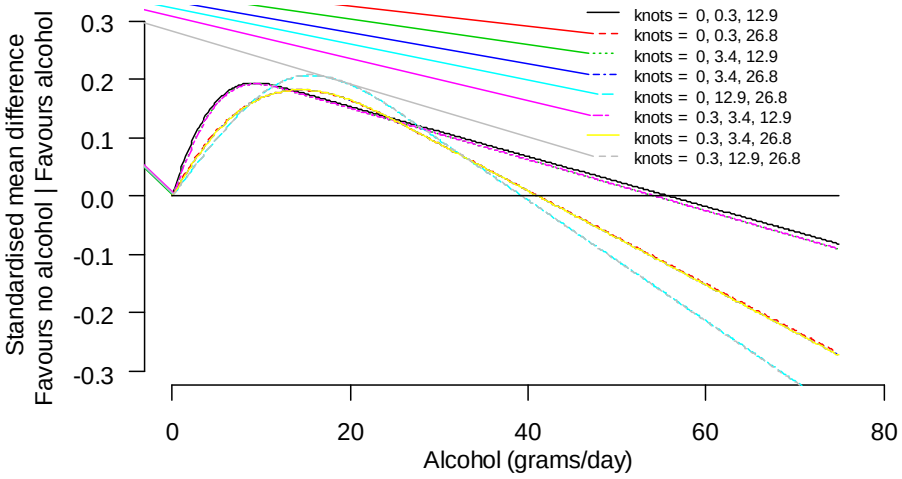

Figure 7.1 Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD using different locations of the three knots in the restricted cubic spline model. The current non-drinker served as the referent group.

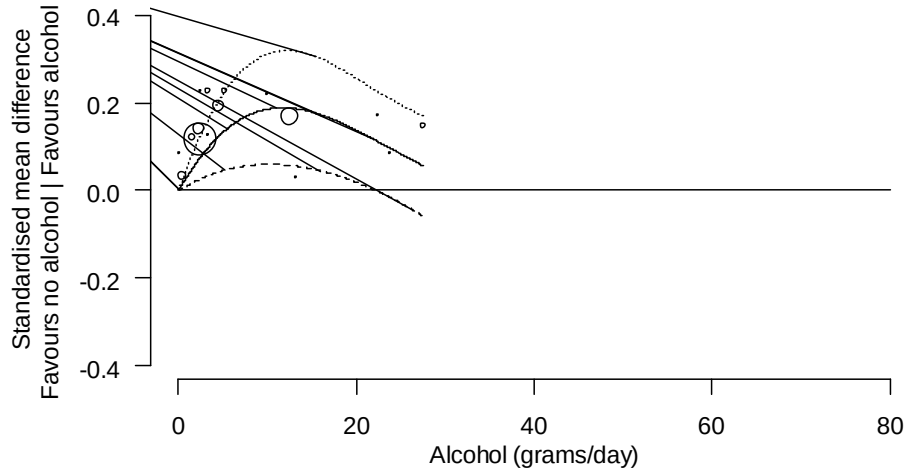

Figure 7.2 Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD with large alcohol consumption values from Kesse-Guyot 2012 (i.e. >30grams/day) removed. The current non-drinker served as the referent group.

Males

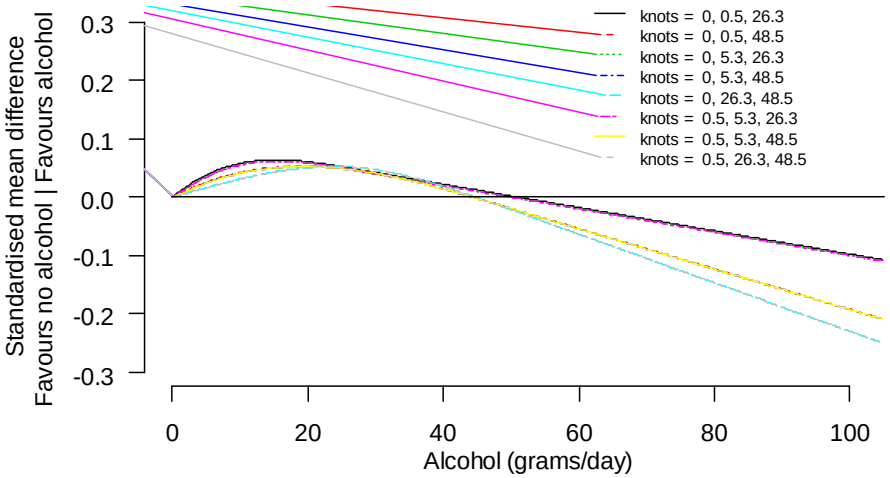

Figure 7.3 Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD using different locations of the three knots in the restricted cubic spline model. The current non-drinker served as the referent group.

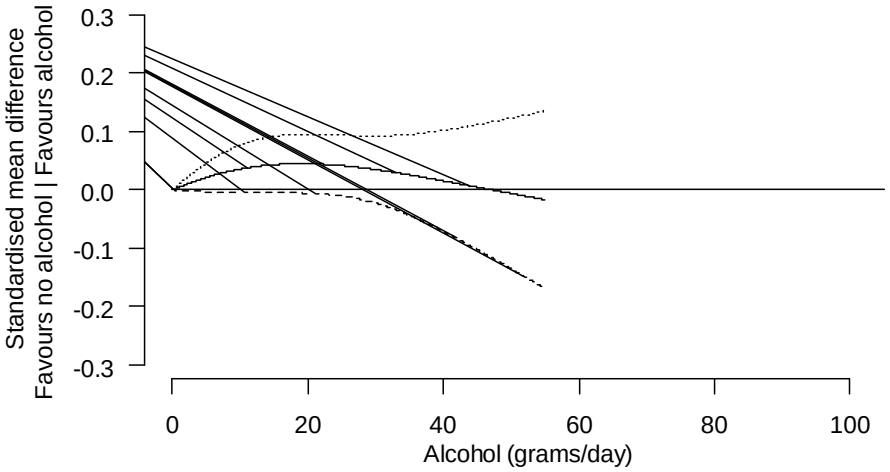

Figure 7.4. Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD with large alcohol consumption values from Kesse-Guyot 2012 (i.e. >70grams/day) removed. The current non-drinker served as the referent group.

Females and males

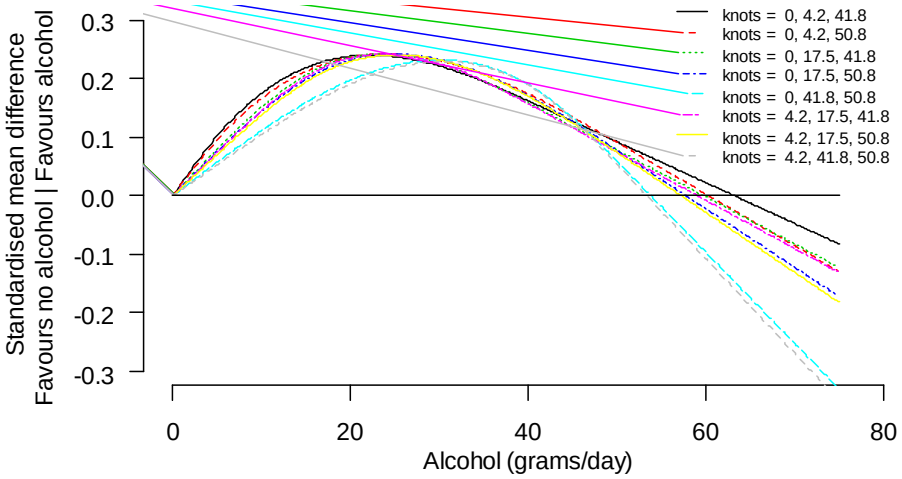

Figure 7.5 Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD using different locations of the three knots in the restricted cubic spline model. The current non-drinker served as the referent group.

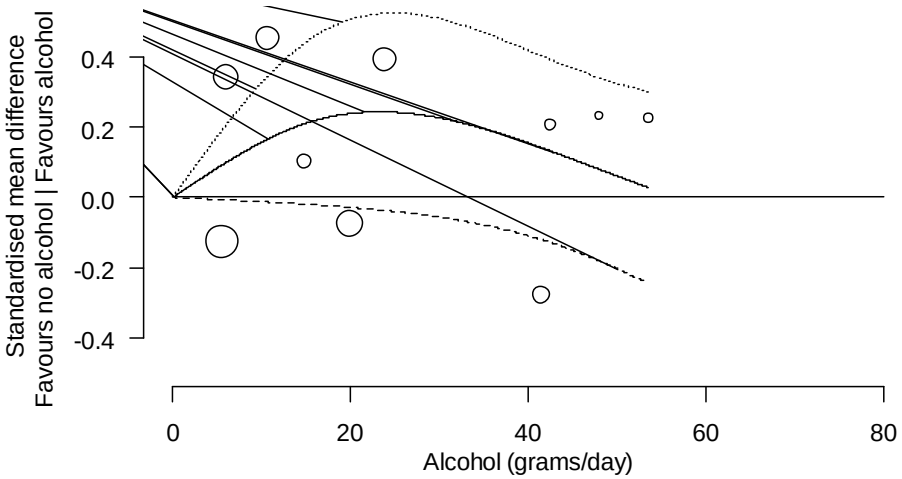

Figure 7.6 Sensitivity analysis of the pooled dose-response relationship between alcohol consumption (grams/day) and SMD with large alcohol consumption values from Kitamura 2017 (i.e. >55grams/day) removed. The current non-drinker served as the referent group.

Appendix 8. Reasons for exclusion of studies from the dose-response analyses

Study ID	Reason for exclusion from dose-response analysis
Hogenkamp 2014	Excluded because the data available for the dose-response analysis are unadjusted means and standard deviations. These statistics do adjust for baseline cognition (through the use of change scores) and age (by design - all participants are the same age at baseline), but do not adjust for other important potential confounders. There is some imbalance in potential confounders at baseline (Table 1).
Lang 2007a	Excluded because the data (ORs and confidence intervals) are only presented in a figure (2). If extracted, a dose-response analysis could be undertaken.
Piumatti 2018	Excluded because the data available for the dose-response are unadjusted means and standard deviations (Table 1), or results from a restricted cubic spline model. The former results are not re-analysed because they adjust for no confounders. The latter results cannot be included in any dose-response synthesis with the other studies because of the data presented. Further, the outcome - reaction time - while providing a measure of cognition differs to the other studies.
Samieri 2013a	Excluded because not all the data are available to undertake a dose-response analysis. Specifically, while mean differences and confidence intervals are provided (Table 2, pg 2), the breakdown of the total sample size (6174) is not provided by alcohol consumption level. This precludes the calculation of standardised mean differences unless some assumptions are made. A single global cognitive function score is the mean of five z-scores (mean 0, variance 1). Thus, the mean and variance of this variable is 0 and 1/5. For the analysis, three measures of cognitive function are averaged, yielding a mean and variance of 0 and 1/(3*5) = 1/15. There is the potential to use the standard deviation calculated from this variance (sqrt(var)) to undertake the dose-response meta-analysis, however we would have to assume the sample sizes were the same across the groups, which is unlikely to be true, and so, the standard errors would be incorrect.
Solfrizzi 2007	Excluded because the metrics presented (from Cox proportional hazards model) are hazard ratios (HRs). When the event is rare (in this case incident mild cognitive impairment), then it may be reasonable to assume that the HRs will yield similar values to Risk Ratios (RR) and in turn ORs (see Sutradhar. Annals of Epidemiology 28 (2018) 54e57) in which case, the data could be reanalysed for the dose-response analysis. The incident cases of MCI during the follow-up period was 105 or 1445 participants. However, we have chosen not to re-analyse this data for the dose-response analysis given the assumptions that would need to be made.
Wardzala 2018	Excluded since it is not clear what effects are being reported from the analysis that could potentially contribute to the dose-response. Specifically, in the online supplement 3, it is not clear whether in the columns 'Drinking-Gender Specific Interactions on Longitudinal Rates', the reported effects are (for example) the average difference in MMSE in the moderate drinkers versus rare/never drinkers at a particular point in time, or the difference in the slope over time between the moderate drinkers versus the rare/never drinkers for a unit of time. Further, the unit of time used in the model is not specified in the statistical analysis section. [JM has contact authors (29/10/2018) to ask some further questions regarding the timing of the alcohol measurement relative to cognition and how to interpret the results presented in the online supplement. No response received as at 23/11/2018.] Note that the results presented in the summary results table, pertain to the analyses that investigate whether the rate of change over time differs across the alcohol consumption groups (that is, those presented in section 'Decline profiles for moderate drinking men and women' (pg 5)).

Appendix 9. Alphabetical reference list of all studies excluded following full text review

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Appendix 10. Abbreviations

95% CI	95% confidence interval
ACE-R	Addenbrooke's Cognitive Examination - Revised
AWC	Alcohol Working Committee
CI	Cognitive impairment
COWAT	Controlled Oral Word Association Test
CVD	Cardio-vascular disease
DSCT	Digit symbol coding test
DSST	Digit symbol substitution test
g	grams
GCF	Global cognitive function
GFQ	Graduated frequency questionnaire
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HVLT-R	Hopkins verbal learning test
MCI	Mild cognitive impairment
MD	Mean difference (usually based on a scale score or test)
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
ms	milliseconds
NHMRC	National Health and Medical Research Council
NIAAA	National Institute on Alcohol Abuse and Alcoholism (United States)
NIA-AA	National Institute on Aging and the Alzheimer's Association (United States)
ONHMRC	Office of the National Health and Medical Research Council
OR	Odds ratio
PECO	Population, Exposure, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses - protocols
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
SCD	Specific cognitive domain
SD	Standard deviation
SE	Standard error
SMD	Standardised mean difference
SR	systematic review
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T0, T1, etc.	Time 0: 1st measurement point; time 1: 2nd measurement point
TICS	Telephone Interview for Cognitive Status
TMT-A & TMT-B	Trail making test part A; Trail making test part B

Appendix 11. Response to comments from the Methodological review, NHMRC and AWC

	Section	Comment (source)	Response
1	Results - studies examining patterns of alcohol consumption Discussion – limitations of the review	**Consider reporting conclusions from studies of patterns of alcohol consumption** (NHMRC/Methods review) Methods review: "… it would be valuable to include the primary study authors' conclusions in the TR, either in Appendix 4 or as a separate table. This would require minimal additional work, as the conclusions could be taken directly from the abstracts, however it would provide some direction for decision-makers on possible conclusions from this body of evidence." NHMRC/AWC: "Ensure [the decision not to examine results from studies examining patterns of consumption] is noted as a limitation in the review."	**Action**: In response to these comments we have provided a more detailed discussion of the limitations arising from not reporting or synthesising results from studies that examined the effects of different patterns of alcohol consumption. We have not extracted or reported conclusions from studies (rationale as follows). Our view, and one which we understood to be widely accepted among systematic review methodologists, is that the only valid way to report results is to independently interpret the analyses and data presented in each paper. Our concerns about the validity of reporting conclusions, and the feasibility of doing so, can be illustrated through our experience with studies examining levels of intake. Of the 16 studies that contributed results data for this question, we confirmed that one study had incorrectly interpreted their analysis and a second study provided no interpretation for the analysis eligible for the review. The latter points to one of the challenges of extracting conclusions (assuming it is valid to do so), since most studies reported multiple analyses (and multiple results from each) including analyses that were ineligible for the current review (e.g. cross sectional, or examining the effect of cognition on alcohol-use behaviours). Given the number and nature of analyses, conclusions are inevitably limited to a small subset of results and may exclude those pertinent to the review question. Assuming the conclusions in the abstract were based on relevant analyses, there is empirical evidence to suggest that conclusions reported in abstracts may be misleading. For example, Lazarus et al examined non-randomised studies of interventions and found 84% (107/128) had at least one example of spin in the abstract, and that "Abstract conclusions of 61 (48 %) articles featured a high level of spin" with selective reporting occurring in 12% of abstracts [35].
2	Results – summary of SR of major cognitive impairment	**Consider summarising and appraising the Xu 2017 SR** (Methods review) "The Xu (2017) review is not summarized or appraised and this would be a helpful addition to the report for completeness"	**Action**: no change (rationale as follows) We agree that a summary and appraisal of the Xu review would provide evidence to address the related question of the effect of different levels of alcohol consumption on major cognitive impairment (dementia). However, our protocol didn't include doing an appraisal or summary of findings (GRADE). Since the scope of the current review was limited to minor cognitive impairment, such a summary could be done separately from the current review.
3	Methods - Search strategy	**Provide rationale for not searching clinical trials registries or grey literature.** (Methods review)	**Action**: no change (rationale as follows) While searching registries is an important safeguard against the impact of reporting bias in randomised trails, guidance in the Cochrane handbook is that it is not clear that registry

	Section	Comment (source)	Response
		AMSTAR Q4: comprehensive literature search strategy "rated as 'partial yes' as there was no search of clinical trials registries or grey literature. Despite this, we consider the search appropriate given the nature of the review"	searches serve an equivalent purpose for cohort studies. Cohort studies are unlike clinical trials, in that they often run over many decades, and collect large of numbers variables that can be used to address a multitude of questions beyond those initially planned when the cohort was initiated (including by researchers not involved in the design or conduct of the cohort study). For these reasons, we felt the value of searching clinical trials registries would be limited. However, in response to the AMSTAR assessment, we searched clinicaltrials.gov for 'cognitive impairment' (condition or disease) AND alcohol (other terms). The search yielded 20 results [23 Nov 2018], none of which appeared relevant to the current systematic review. In respect of searching the grey literature, the term is variably applied so as to have little intrinsic meaning. Our preference is to specify the forms of 'literature' being sought (e.g. trial registrations, theses, conference proceedings, government reports, etc.), the sources to be searched and the strategies to be used to search these sources. For this review, we considered that searching beyond bibliographic databases would be unlikely to yield additional useable information, particularly given the rationale above and the high number of studies included in the review.
4	Results - Characteristics of included studies	**Consider reporting sources of funding for each study.** (Methods review) AMSTAR Q10: sources of funding. "Although the authors state that they extracted the sources of funding for each included study (EER, p15), we are not able to locate this information in the EER or TR."	**Action:** New table added to Technical report (Appendix 4: Table 4.2. Funding sources, potential conflicts of interest, and ethics approval for studies that examined different levels of alcohol consumption), and assessment summarised (SR report, Section 4.3). We had omitted this information from the draft report; however, data on funding, conflicts of interest and ethics was collected for the review (see *Methods* for the SR). We have now collated and reported this information.
5	Discussion - Limitations of the SR	**Discuss implications of the assumptions and transformations made for analysis** (Methods review; NHMRC) MR "A discussion of some of the decisions made in the analysis, and the impact of these, might be useful in the discussion of the limitations of the review. For example, the impact of the many transformations and assumptions (Appendix 2, TR) on certainty of the findings and the combining of multiple outcome measures using standardised mean difference	**Action:** In response to this suggestion, we have provided a more detailed discussion of the limitations arising from the assumptions made in order to be able to *standardise alcohol consumption* and *effect measures* (or measures of association) across studies (SR report *Discussion*). Importantly, standardising alcohol consumption and effect measures is a necessary step for enabling comparisons of findings across studies, irrespective of whether results are then pooled in a statistical analysis or not. Hence, any limitations arising from standardisation apply whether we report results from single studies, pool results in pairwise meta-analyses (i.e. examining whether cognitive function differs with one level of alcohol consumption compared to another, for example <10 g/week versus ≥ 20 g/day to <30 g/day), or pool results in a dose-response analysis (i.e.

	Section	Comment (source)	Response
		(both briefly touched on in EER, p48)." NHMRC "Given the limitations you refer to in assessing and reporting on the dose response (4.4.1) ... perhaps just investigating and reporting on [pairwise] association[s]" might have given us more fruitful (less limitations) results?"	examining whether cognitive functions differs with increasing levels of alcohol consumption).
6	Results - Evidence profile (Table 7)	**Reconsider GRADE for dose response result for men and women (combined)** (NHMRC) "Looking at the evidence profile at Table 7, …should the certainty for cognition (men and women) be classed as low, not very low, given the rating should have only dropped by 2 for very serious ROB. The other two outcomes above this one seem appropriately downgraded by three points for serious ROB and inconsistency."	**Action**: change to downgrade by -1 for inconsistency; no change to overall GRADE. We agree, the GRADE assigned was inconsistent with the footnoted assessment of each domain. While there the I^2 value is lower for this result than the other two dose response analyses, and the P value for the test of heterogeneity >0.05, the difference in statistical heterogeneity between this result and the other two dose-response analyses is marginal. Given the result has some imprecision, for which we had not downgraded, we have revised our footnoting to confirm downgrading for inconsistency, with an overall GRADE of VERY LOW certainty.
7	Methods & results - Evidence profile (Table 7)	**Consider writing evidence statements using NHMRC decision rules** (Methods review, NHMRC) Methodological review: "No formal evidence statements are provided" NHMRC: "Evidence statements based on GRADE outcomes would ensure consistency across all review reports."	**Action:** Change made. We have included an evidence statement in the format suggested by the NHMRC. In the methods section we have added a description of the decision rules used to formulate these statements. Note these decision rules have been modified to align with GRADE definitions / decision rules, and the minimum requirements for claiming use of the GRADE. We have included information about the size and direction of effect in the text following the statement, as required when summarising findings using GRADE methods.
8	Discussion – limitations of the review	**Note the implications of excluding studies that analysed concomitant measures of alcohol and cognition at follow-up** "Excluded studies determined to be high quality with possible useful information. Studies excluded based on agreed criteria." "Add exclusion criteria in report limitations, citing outside scope of review."	**Action:** In the section on Excluded studies, we have clarified that the analysis in these studies was such that causal inferences could not be made about the effect of alcohol on cognition. In our tables of excluded studies (Technical report, Appendix 5) we highlight these studies, and a range of other evidence that falls outside the scope of the review, noting its potential to inform the guideline more broadly. We have not added anything to the review limitations, since the studies aimed to address a different question from that specified for the review. This misalignment is a commonly encountered scenario in reviews, but not a limitation of the review or the primary evidence.
9	Results – outcomes measures	**Clarify outcomes measured in studies contributing to dose response analyses** (AWC)	**Action:** In the text describing results from the dose response analyses (SR report, Section 4.4.1), we have added a description of the types of outcomes measured in each of the

	Section	Comment (source)	Response
	included in dose response analyses	"There were three different types of outcomes across the 18 studies: diagnosis, specific cognitive functioning tests and global functioning. Were all three mixed up in the summed/average/single dose-response curves?" " … how many studies were included and did they differ on the outcome measure type (cognition)?"	studies included in the dose response analyses. The outcomes included in the analysis were different for each study (with differences in the type of outcome, the measurement method or both). For this reason, we were unable to undertake sensitivity analyses to determine if results differed depending on the outcome measure.
10	Methods – exclusion of studies based on high level alcohol intake	**Clarify rationale for exclusion of studies that examined only high levels of alcohol intake** "Why is [examining the effects of high levels of alcohol consumption] grounds for exclusion?"	We excluded studies in which the only comparison was high levels of alcohol consumption (above the upper category specified for the review ≥50 g/day) versus a single lower-level category (generally defined as anything less than the high intake category). The reason for this was that most of the studies were among people with a current or prior alcohol-use disorder, and we felt that quantification of the upper bound of intake was unlikely to be possible, and hence average consumption could not be quantified.
11	Results – PRISMA flow diagram	**Check numbers in PRISMA flow diagram** PRISMA flow diagram: question about tally of studies in the SR.	We confirm that the numbers are correct. We have used the standard convention for reporting a PRISMA flow diagram, which reports total studies included in the systematic review (n=25) separately from the subset included in the quantitative summary and synthesis (n=16). Since the studies excluded from quantitative synthesis are retained in the review, they are not listed in the column reporting exclusions.
12	Excluded studies	**Provide list of Mendelian randomisation studies** (NHMRC/AWC)	We excluded two Mendelian randomised studies that appeared to meet most eligibility criteria. These are listed in the Technical report, Appendix 5, Table 5.12
13	Typographical errors and other minor changes	**Correct typographical errors** (Methods review; AWC - PD) P4, heading. Change 'protocol' to 'report' or 'systematic review' P5, last sentence. Add 'function' P8, last sentence. Remove 'measure' P12, second sentence. Remove 'will' P14, 3rd paragraph. States 'no language or geographic limitations were applied' however, p13 states 'studies published in languages other than English were excluded.' P14, 6th paragraph. Remove 'been' P15, 5th paragraph. Remove 'be'	**Action**: We have corrected the identified typographic errors, and provided clarification below in relation to two comments. *P14, 3rd paragraph. States 'no language or geographic limitations were applied' however, p13 states 'studies published in languages other than English were excluded.'* This is correct; no language limitations were applied to the search, but we only included English language studies when screening. We have added "to the search" at the end of the sentence on p14. *P40, figure 4. Sabia 2011, X-axis appears too short.* This change is difficult to make due to limitations of the R program. We think that the current presentation is unlikely to affect interpretation, so have not changed the figure.

Section		Comment (source)	Response
		P15, 1st dot point. Remove 'be' P18, 1st paragraph. Remove 'the' in first sentence. Check wording of second sentence. Add details of the cross reference to the Appendix (i.e. Appendix number) P19, 3rd last paragraph. 'we dose value assigned was calculated' is unclear P20, 3rd paragraph. Remove 'only' P21, 5th paragraph. Missing reference. P23. Two broken cross references. P24, 1st paragraph. Replace 'studies' with 'students' P30, Kitamura 2017. RoB is missing. P32, Piumatti 2018. RoB is missing. P40, figure 4. Sabia 2011, X-axis appears too short. P47, 4th paragraph. Add 'of' to 'could be use in' AWC: Additional errors as marked-up on a copy of the draft report.	

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