

SYSTEMATIC REVIEW

Alcohol, dementia and cognitive decline in the elderly: a systematic review

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Abstract

Background: dementia and cognitive decline have been linked to cardiovascular risk. Alcohol has known negative effects in large quantities but may be protective for the cardiovascular system in smaller amounts. Effect of alcohol intake may be greater in the elderly and may impact on cognition.

Methods: to evaluate the evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption, a systematic review and meta-analyses were carried out. Criteria for inclusion were longitudinal studies of subjects aged ≥ 65 , with primary outcomes of incident dementia/cognitive decline.

Results: 23 studies were identified (20 epidemiological cohort, three retrospective matched case-control nested in a cohort). Meta-analyses suggest that small amounts of alcohol may be protective against dementia (random effects model, risk ratio [RR] 0.63; 95% CI 0.53–0.75) and Alzheimer's disease (RR 0.57; 0.44–0.74) but not for vascular dementia (RR 0.82; 0.50–1.35) or cognitive decline (RR 0.89; 0.67–1.17). However, studies varied, with differing lengths of follow up, measurement of alcohol intake, inclusion of true abstainers and assessment of potential confounders.

Conclusions: because of the heterogeneity in the data these findings should be interpreted with caution. However, there is some evidence to suggest that limited alcohol intake in earlier adult life may be protective against incident dementia later.

Keywords: elderly, dementia, cognitive decline, alcohol

Introduction

Despite chronic alcohol abuse causing progressive neurodegenerative disease [1] several studies have suggested that alcohol consumption, within limits and/or of certain types, is associated with a decreased risk of dementia or cognitive decline. There are many mechanisms proposed in the literature to explain this. It has been suggested that the antioxidant properties of the flavonoids in wine may help prevent the oxidative damage implicated in dementia [2–4]. Alcohol also increases levels of HDL cholesterol and fibrinolytic factors leading to lower platelet aggregation and possibly lower risk of stroke/ischemia [5, 6]. At least one study has found that light to moderate alcohol intake (one drink per week to four drinks per day) is associated with a lower prevalence of vascular brain findings on imaging and less atrophy of the hippocampus and amygdala in APOEε4 carriers as assessed by magnetic resonance imaging (MRI) [7].

The consumption of alcohol has also been associated with decreased cardiovascular risk via the mechanisms described above and possible enhancement of insulin sensitivity or reduction in inflammatory response [5, 8, 9]. Given the link between vascular dementia (VaD), vascular function, and the increasing body of evidence suggesting that Alzheimer's disease (AD) may be influenced by vascular factors, [10–19] it may be concluded that this cardiovascular protection decreases incident dementia/cognitive decline. Counter to this are the effects of heavy alcohol consumption and alcoholism as detrimental to memory function [1].

While most evidence is derived from studies of younger adults, the possible protective effects of alcohol may also apply to older adults, i.e. those at greatest risk from dementia. Lower levels of alcohol intake have proportionally greater effects in the elderly, due to their decreased lean body mass and lower percentage of body weight made up of water [20]. Alcohol may also have negative impacts on other body systems in this age group and may be the cause of falls,

with potentially more serious consequences than in younger people, although the evidence for this is not clear cut [20, 21].

Nevertheless, we are not certain whether regular alcohol intake protects against incident cognitive decline and/or dementia in the elderly and if so what level of intake would be preferred? There are issues related to this research subject with regard to the practicalities of answering this question. As it would be neither ethical nor feasible to carry out a randomised controlled trial with alcohol as a dose controlled intervention, epidemiological methods are a less robust alternative option. A systematic review of all the available appropriate evidence may provide a robust and pragmatic way of answering this research question. Three existing systematic reviews have focussed on psychotherapeutic approaches to AD [2], health-related effects of alcohol use in older people [20] and risk factors for functional status decline [22]. We have therefore carried out a systematic review covering articles published since 1995 when the most recent update of the Diagnostic and Statistical Manual for mental disorders edition IV (DSMIV) was published. As dementia is most prevalent and incident in older people, the review was limited to participants aged 65 years and over. Dementia of specific types can be hard to diagnose pre-mortem; therefore the review included unspecified dementia in addition to AD and VaD (both prevalent in the elderly) [23].

The objective was to evaluate the relationship between alcohol consumption and incident cognitive decline/dementia in the elderly via a systematic review.

Method

Search terms 'alcohol' or 'wine' or 'beer' and 'dementia' or 'VaD' or 'multi-infarct dementia' or 'AD' or 'cognitive impairment' or 'cognitive decline' were used as keywords and the databases Medline, Embase and Psycinfo were searched for English language publications relating to human populations and occurring between 1995 and March 2006. When available, standard search categories were also used that matched the above terms. All searches were limited to subjects aged 65 years and above. Two reviewers with experience in methods and content appraised all abstracts and subsequently all chosen studies, independently. Any discrepancies in decisions were discussed to achieve a unanimous choice of articles. No hand searching was carried out.

Quality was assessed using standard criteria assessing key factors including appropriate design, recruitment, analysis and provision of suitable information relating to key aspects of the study [24]. Case studies, letters, consensus opinion from conferences and expert opinions or editorials were not included. Studies with inadequate definition of the outcomes of interest were also excluded. In order to aid investigation of causality, only longitudinal studies were included in the final selection and their content was summarised in extraction tables independently by the two reviewers. To be eligible for inclusion in the meta-analyses, studies had to compare alcohol intake (yes, or defined dose) versus none

(no, or baseline amount) against an outcome of dementia or cognitive decline. A random effects model was used as this provides a more conservative approach, and tests for heterogeneity of the data were carried out.

Results

From the selected abstracts, 94 papers were obtained for further review, and of these, 26 papers reporting on 23 studies were included here. Studies were assessed according to their methodology as above although only epidemiological studies were found. There were no randomised controlled trials and no studies employed blinding, randomisation or controlled intervention. Only longitudinal studies were considered as these are best placed to identify any causal protective/detrimental effect that alcohol may have on cognition.

Of the 26 identified papers [25–50], 22 were epidemiological population cohort studies and 4 [25, 26, 38, 44] were retrospective matched case–control-based assessments nested in cohort samples. In at least one study [30] alcohol intake and dementia/cognition was not a primary focus. For one study, two papers were published based on the same population and reported similar results [49, 50]. For two further studies, different populations were described in each pair of publications, with different follow-up periods also in one pair of papers. Each of these two studies was represented by two papers detailing outcomes [26, 38, 29, 35]. When the papers were assessed using standard criteria including assessment of study design and reporting standards, all studies achieved scores of 15 or higher out of a possible 22 [24]. Points were lost mainly for potential bias in subject selection, inadequate baseline information or lack of detail in results.

In this paper, therefore we systematically review 26 papers, representing 23 studies, reporting on 25 different sets of results. Follow-up length varied from 1 to 25 years with most studies having more than 5 years of follow-up. Mean follow-up times for two studies were less than 2 years [27, 28]; ten studies, 2–5 years [26, 29–34, 36, 38, 41]; eight studies, 6–10 years [25, 35, 39, 40, 42, 43, 49, 50]; and six studies more than 10 years [37, 44–48]. It was not always possible to establish mean/median ages or age ranges as these were not reported consistently. The vast majority of the studies were from Europe, particularly northern Europe or from North America/Canada.

Definitions of outcomes varied with five studies reporting on dementia [30, 37, 45, 46, 48]. Three studies examined AD alone [32, 38, 43], three AD and dementia [29, 35, 44], two VaD [26, 49], one AD and VaD [31] and two all dementia, VaD and AD [25, 42]. Eleven studies assessed cognitive decline [27, 28, 30, 33, 34, 36, 39–41, 47, 48].

Fifteen papers (14 studies) found one or more statistically significant association with alcohol intake; three studies found an increased risk for either VaD [49], AD (when place of residence only was controlled for) [32], dementia as a whole or poorer performance on a visual reproduction test [36]. The remaining 11 studies were positive, with one

finding that reduced cognitive function was associated with abstinence before age 60 [40].

The reported results from all included studies as relative risks, odds ratios or hazard ratios were collated for meta-analyses in accordance with their outcome: dementia, AD, VaD and cognitive decline respectively. Two studies reported results as mean change scores [36, 41] and were not included in the meta-analysis. Although tests for heterogeneity proved to be statistically significant for each outcome ($P = 0.013, P = 0.035, P = 0.041, P < 0.0001$) forest

plots were generated using a random effects model in order to allow graphical representation of the findings (full details can be found in Appendix 1 and Appendix 2 in the supplementary data on the journal's website <http://www.ageing.oxfordjournals.org>). Using a fixed effects model produced similar results. The combined risk ratios for each of the four outcomes were dementia 0.63 (95% CI 0.53–0.75), AD 0.57 (95% CI 0.44–0.74), VaD 0.82 (95% CI 0.50–1.35) and cognitive decline 0.89 (95% CI 0.67–1.17), respectively with alcohol intake. Figure 1 shows

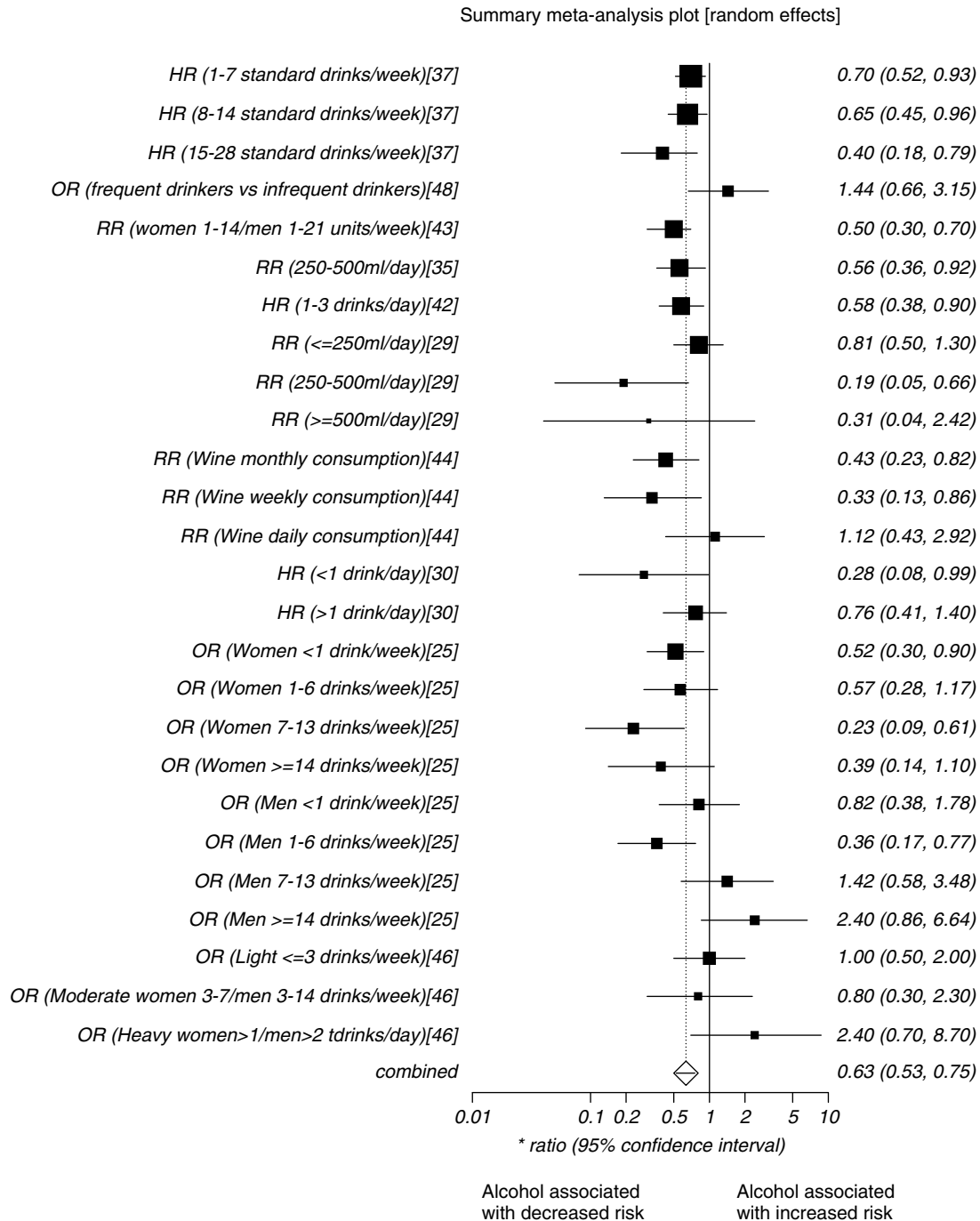


Figure 1. Dementia and alcohol.

the studies with dementia as an outcome; Figure 2, those that specified AD; Figure 3, VaD; and Figure 4, cognitive decline. Logarithmic scales are used in order to summarise all the data within the confines of the figures. Some studies provided data for multiple sub-groups and this information is also included wherever possible. Some studies also looked at more than one outcome and so appear in more than one graph. In order to take the most conservative view, where available, the values used in the meta-analyses were from modelled data, adjusted by the individual authors for confounding. To summarise, alcohol consumption appears to be protective for dementia and AD, but there is no evidence of a protective effect against VaD or impaired cognitive function.

Alcohol consumption: optimal consumption and alcohol type

With regard to cognitive function, results for optimal consumption were mixed, either above/below or equal to one drink a month or day [30, 39] (in subjects with cardiovascular disease or diabetes, one–two drinks per week [41]). For AD, optimal amounts were a weekly consumption of wine [38], one–six or more than two drinks per week [25, 29], or more than three drinks/250–500 ml per day (usually wine) [35], or where studied by gender, one–three per day in males [29, 35, 42]. For dementia, benefit was shown for more

than one drink per day, weekly or monthly wine consumption, 250–500 ml (usually wine) or more than three drinks per day [29, 30, 35, 44] and from 1–28 units per week [37]. For VaD, one–three drinks per day in males [42] was beneficial. In summary, there was no close agreement among studies as to the optimal level of consumption and although most studies reported that light to moderate consumption was best with regard to incident decline or dementia the classification of light to moderate drinking varied very widely.

With regard to the alcohol type, 12 studies looked at beers, wines and spirits separately [25, 28–32, 36, 38, 42–44, 46] although for two, only wine was consumed in any quantity by the study population [29, 32]. One study reported examining red and white wine separately in their questions but did not report in detail regarding this [28]. In four papers (two from the same population but with a different follow-up [29, 35]), wine intake was found to significantly reduce the risk [29, 35, 38, 44].

Methodological considerations

Effects of non-participation due to death during follow-up or other causes

Three studies took account of the effect of death on outcome [25, 29, 38]. Survivors may be less cognitively impaired and constitute higher functioning participants.

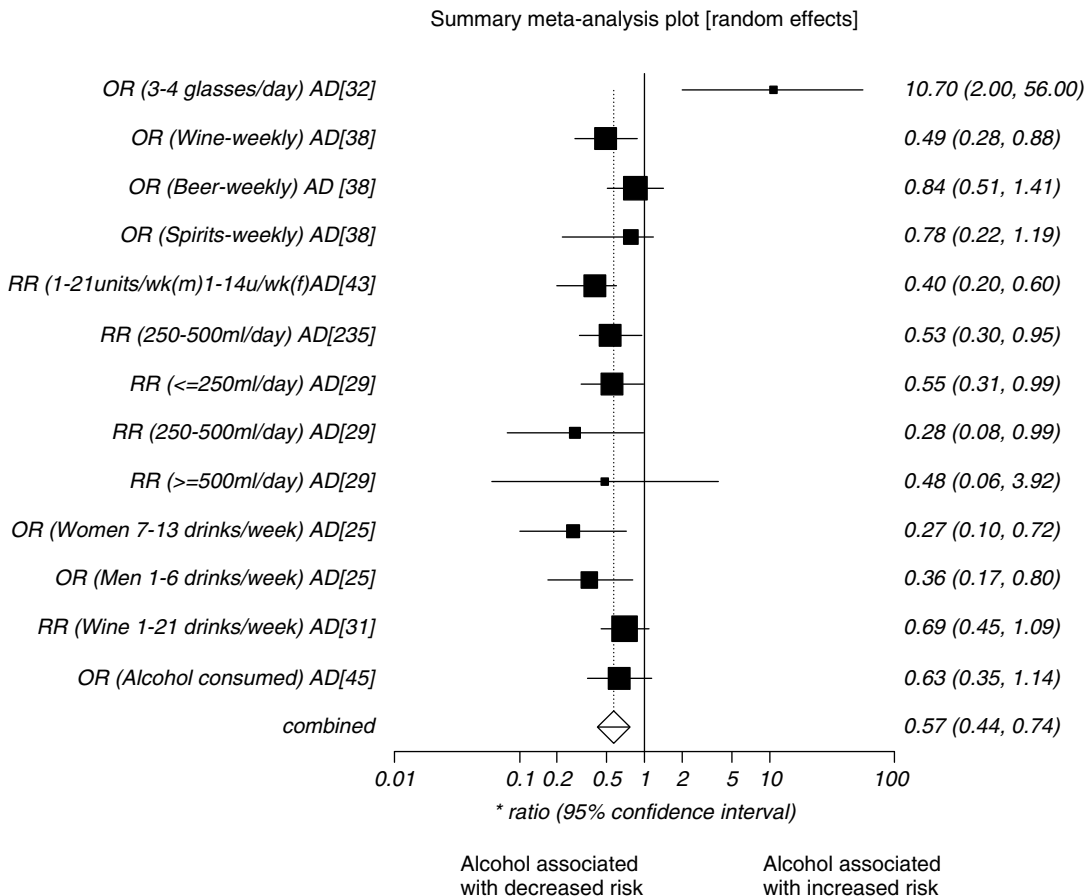


Figure 2. AD and alcohol.

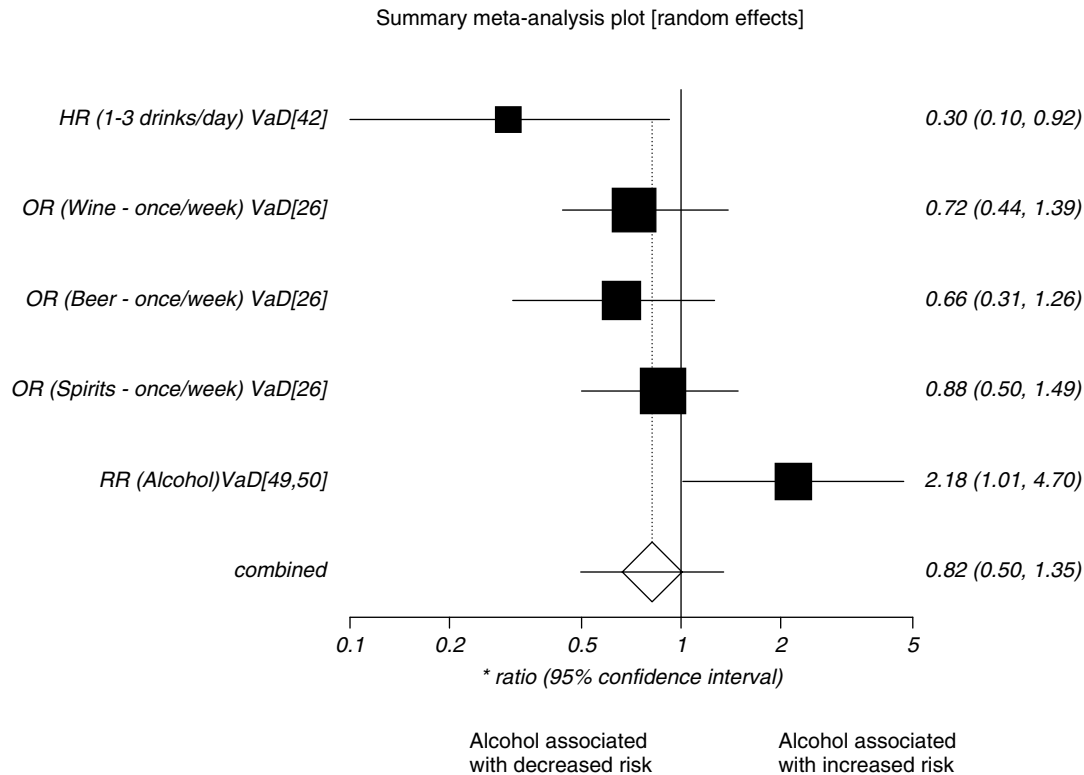


Figure 3. VaD and alcohol.

Six studies compared participants with non-participants. Four found no significant differences [29, 40, 41, 46] and two that non-participants were significantly older, [44] less educated and with higher levels of cardiovascular risk [48].

Quantity of intake and change in intake over time

All except one study used categories of consumption though these could be as basic as use/not use alcohol. The reference category used was '0', i.e. non-drinkers in the vast majority of studies and although several stated that they asked participants if they had drunk 'ever/never' only a few accounted for reported abstainers/quitters in more detail [25, 28, 39, 46, 47]. In three studies the reference category included low-level drinkers, less than or equal to one drink a week [29], less than one drink per week [43], or infrequent/less than one drink per month [48]. The time period over which alcohol intake was assessed also varied.

Characteristics of drinkers

Ten studies reported other differences between drinkers and non-drinkers, with drinkers more likely to be current/ex smokers [30, 39, 42, 43, 48], have higher income, educational/occupational attainment [29, 32, 33, 42, 43, 48], live with others, be male [29, 32, 33, 42, 44, 48], have no history of cardiovascular disease, diabetes, hypertension and depression [29, 30, 33, 41, 43], be Caucasian [30], younger [48], have lower [30] or higher body mass index [29], use 'psychotropic drugs' [29, 33], and for women, to have used hormone replacement treatment in the past [30],

and have better subjective health scores (men and women) [29].

There was also a wide variation in the reporting of factors adjusted for in-analyses. Five studies stated that they controlled for baseline cognitive function in their analyses [27, 29, 33, 39, 40] but detailed information was not available for all studies and it is possible that additional confounders were present and uncontrolled for.

Discussion

An examination of all research published within the last 10 years suggests that, at least in epidemiological studies, low to moderate alcohol use is associated with a 38% reduced risk of unspecified incident dementia. For AD also, low to moderate alcohol was associated with a significantly reduced risk of 32%. Although the point estimates are also in a similar direction for VaD and cognitive decline (0.82 and 0.89 respectively), the results were not statistically significant. All of these results should be interpreted carefully given the significant heterogeneity of the available studies and the long time scale and insidious onset of dementing illnesses. Publication bias may have resulted in negative studies not being published, although this was not indicated by funnel plots and bias indicators were non-significant. The differences seen between the significant results in unspecified dementia and AD as compared to VaD and cognitive decline may be due to the small number of studies, only five, reporting VaD as an outcome and to the difficulties in the classification of pure VaD and cognitive decline. It could be

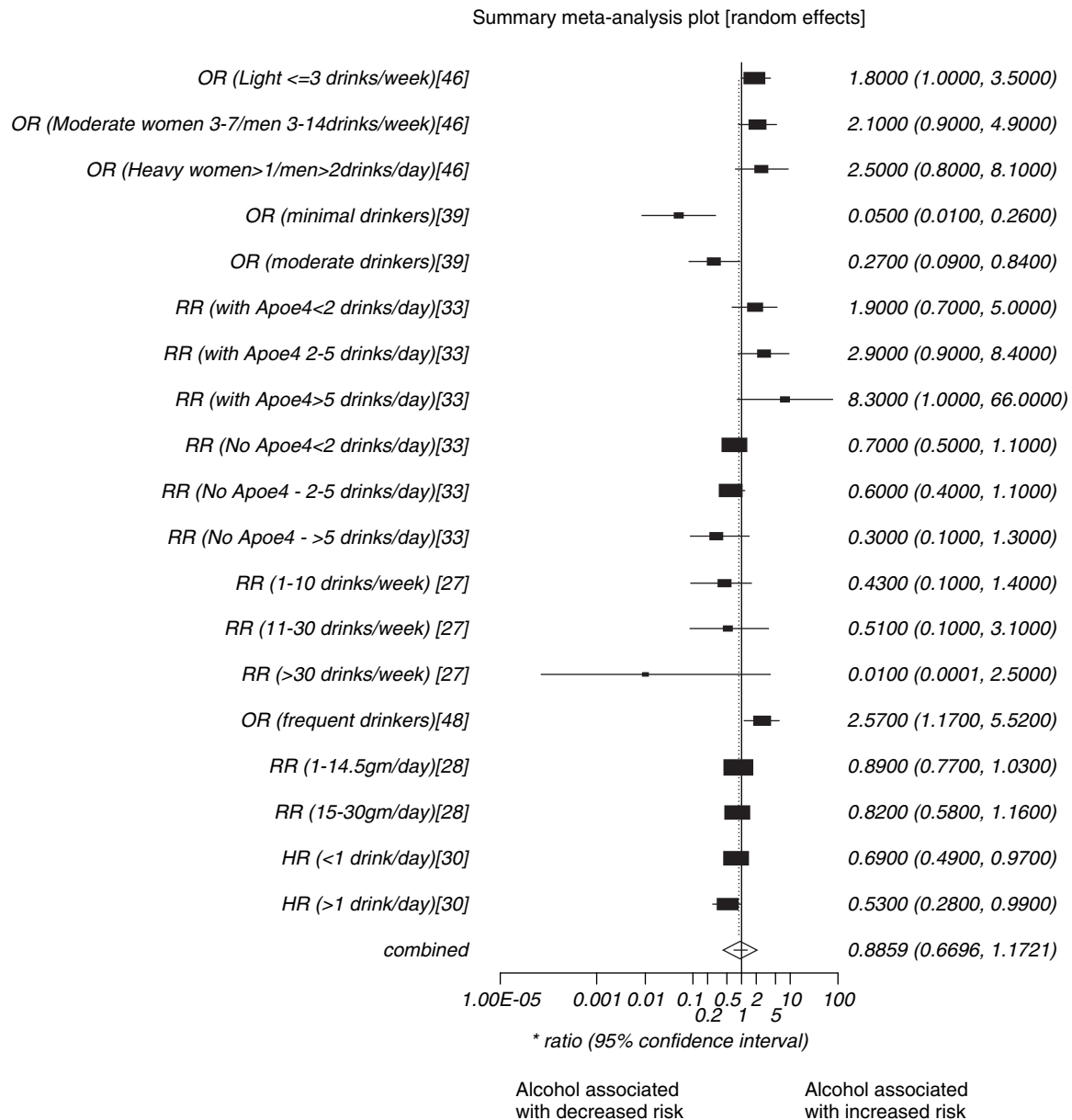


Figure 4. Cognitive decline and alcohol.

argued that unspecified dementia is the stronger endpoint. On the other hand, the protective effects of alcohol are thought to have cardiovascular mechanisms at least in part and it may be expected to have an even greater effect on VaD. Further confounding comes from the different ways that AD and VaD are classified with studies often including cases with vascular factors in the AD category.

The difficulty lies in trying to clarify this issue further. The different studies vary in population, assessment, follow-up, and classification of alcohol use with some studies not specifying the amount of alcohol in a ‘standard drink’, a value that can vary by country [51]. Also related to this is the repeated finding that it is the low to moderate levels of alcohol that are protective despite the amounts included in this category varying widely between studies. It may be

that the part of the population studied who drink what are moderate levels of alcohol for their societies also practise moderation in other areas and may be healthier generally than those who do not. With respect to alcohol intake, the amount of detail reported regarding the collection of these data also varies widely with some studies collecting data on recent consumption to some assessing consumption further back in time or lifetime abstinence/change in consumption and with the ‘non-drinker’ reference category, at least for three studies, allowing for some consumption. This may be particularly pertinent in the elderly as people may reduce consumption as they age [51] although not all studies agree with this [20, 42, 46]. It may be that the prevalence of binge drinking has only increased recently, especially for women, but it is surprising that so few studies assessed this in

their participants. It must be remembered also that the participants in these studies will suffer from cohort effects with exhaustion of susceptibles and that traditionally men drank far more than women. Gender was adjusted for in many of the studies as were a variety of other factors although these too ranged widely.

The attempts made in some studies to examine the topic in more detail, looking at specific dementia type, alcohol type, gender or APOEε4 status seemed to suggest that the protective effects are more likely with wine consumption and the absence of an APOEε4 allele, although many studies suffered from small numbers of cases in their sub-groups. The ‘j’ shaped curve was seen in majority of the studies although with wide confidence intervals and lack of significance. Given the possibility that red wine rather than white may provide most protection, although the evidence is slight [52], it is unfortunate that no studies reported specifically on this although small numbers and changing trends in alcohol type preference may account for this.

The results of a recent meta-analysis looking at mortality and alcohol suggest that the protective effects have been over-estimated due to the diversity of the studies involved and the lack of accounting for loss in follow-up. This allowed for past drinking in the non-drinker comparator group. There was also a lack of standardisation regarding the alcoholic amount consumed [51]. It is not clear whether this would also apply to cognitive function but it is clear that there are at least two studies that are not subject to the pitfalls described in the above meta-analysis and which did show positive beneficial findings for alcohol [25, 39].

Although alcohol may be associated with less incident dementia, we are far from being able to infer causality and it could still be that participants who drink alcohol sensibly also moderate themselves to live healthier lives both in physical, dietary and mental perspectives. Certainly in the studies that reported the characteristics of the drinkers they appear to do so. Increasing evidence also points to lifestyle practices impacting on cognition, such as exercise, and diet, such as fish, vitamin E and antioxidant consumption [53–56], not all factors of which were adjusted for in the studies examined. Educational level is also known to affect at least identification of cognitive decline although how this occurs is still unclear [57–61].

As it is highly unlikely that it would ever be possible to carry out a randomised placebo controlled trial in this area, it may never be feasible to answer with absolute certainty the question of whether alcohol consumption may be protective. Other techniques such as observing protective effects in populations who metabolise alcohol at different rates (for example, comparing Asian and Western populations) may shed further light on this area. Judging from the publications of robust longitudinal studies available here it would seem that mild to moderate alcohol intake is associated with less incident dementia, at least in Western populations. However, the proviso should always be that alcohol is consumed within a healthy lifestyle and with moderation.

Key points

- In older people, small to moderate amounts of alcohol consumption are associated with reduced incidence of dementia and Alzheimer’s disease (AD).
- The evidence is strongest for wine consumption but not conclusive.
- As intervention studies are not feasible in this area, the best evidence comes from an overview of longitudinal studies despite some individual methodological limitations.

Supplementary data

Supplementary data for this article are available online at <http://ageing.oxfordjournals.org>.

References

(Due to the large number of references, only 40 are listed below and are represented by boldtype throughout the text. The full list can be found in the supplementary data online, on the journal website <http://www.ageing.oxfordjournals.org> as Appendix 3.)

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