Critique 197: Alcohol consumption and the risk of developing dementia - 13 March 2017

Xu W, Wang H, Wan Y, Tan C, Li J, Tan L, Yu JT. Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. Eur J Epidemiol 2017;32:31-42. doi: 10.1007/s10654-017-0225-3. Epub 2017.

Authors' Abstract

It is widely believed that light-to-moderate alcohol intake may protect against dementia while excessive drinking may instead increase the risk. Nonetheless, these findings need cautious interpretations due to varying methodologies and lack of standard definition, which hindered our transferring into preventative practice.

The objective of this study is to investigate the potential dose-response association between alcohol consumption and risk of dementia. A systematic search was conducted in electronic databases to identify relevant studies. Risk estimates were combined using a random-effect model. Eleven studies with 73,330 participants and 4586 cases for all-cause dementia (ACD), five studies with 52,715 participants and 1267 cases for Alzheimer's dementia (AD) and four studies with 49,535 participants and 542 cases for vascular dementia were included.

We observed a nonlinear association between alcohol consumption and ACD risk (p nonlinearity < 0.05). The alcohol dose associated with lower risk of dementia was confined to at most 12.5 g/day, with the risk hitting bottom (RR ≈ 0.9) at roughly 6 g/day. Of note, the ACD risk seemed to be elevated (≈10%) when the dose surpasses certain levels: 23 drinks/week or 38 g/day. For the alcohol type, recommendation for wine is prioritized. The subgroup analysis further indicated that the effect of alcohol may be greater in younger adults (<60 years old) with regard to fighting against dementia. Modest alcohol consumption (≤12.5 g/day) is associated with a reduced risk of dementia with 6 g/day of alcohol conferring a lower risk than other levels while excessive drinking (≥38 g/day) may instead elevate the risk.

Forum Comments

Data from essentially all prospective population studies have shown that there are protective effects of moderate alcohol consumption against the development of cardiovascular disease and total mortality. This relation has been described as a "J-shaped curve," with a lower risk of disease for moderate drinkers in comparison with non-drinkers, but an increase in risk for heavy drinkers. An increasing number of reports have also suggested a J-shaped curve for the relation of alcohol consumption to the risk of dementia, including Alzheimer's disease. In a previous meta-analysis on alcohol and cognition in 2011, Neafsey & Collins reported: "The average ratio of risk for cognitive risk (all forms of dementia or cognitive impairment/decline) associated with moderate drinking of alcohol was 0.77, with nondrinkers as the reference

group; both light and moderate drinking provided a similar benefit, but heavy drinking was associated with nonsignificantly higher cognitive risk for dementia and cognitive impairment. Although the meta-analysis also indicated that wine was better than beer or spirits, this was based on a relatively small number of studies."

Experimental studies in animals and limited human studies seeking a mechanism for a protective effect of moderate drinking for dementia have suggested decreases in cerebral atherosclerosis, direct protective effects on the brain, and decreases in inflammation (as described in depth below in this critique).

The present meta-analysis was based on data from 11 studies with 4,586 cases of all-cause dementia diagnosed among more than 70,000 subjects and two additional analyses of studies of approximately 50,000 subjects each for evaluating the association of alcohol intake with the diagnosis of Alzheimer's disease and for vascular dementia. Seven studies provided results according to type of alcohol consumed, while two provided results according to APOE 4 polymorphisms.

The conclusions of the authors are that light-to-moderate alcohol consumption was associated with lower risk of all types of dementia, with beverage-specific analyses indicating that the effect was primarily for wine. There was a suggestion of increased risk of dementia with heavy consumption of total alcohol. The authors state that the risk of dementia is lower for the consumption of up to 12.5 g of alcohol/day (about one typical drink/day), and risk was increased for consumers of more than 38 g/day (about 3 to 4 typical drinks/day).

Specific comments by Forum members

Forum members thought that this meta-analysis had a number of strengths: it is based only on prospective epidemiologic studies from Europe, the USA, or China; the quality of all studies was very good (ranked 8 or greater on a scale of 1-9); and appropriate statistical testing was used, including restricted spine models to judge non-linear associations. Further, sub-analyses were done for two categories of age (< 60, ≥ 60), with slightly better effects being found for subjects < 60 years of age. Another strength of the analysis was that effects were tested according to the presence or absence of the APOE 4 polymorphism (it turned out that estimates for all levels of drinking were essentially the same regardless of the presence or absence of APOE 4).

It was important that effects were measured by type of beverage consumed, as in this meta-analysis beneficial effects were seen only for wine. Forum member Ellison commented: "Light-to-moderate wine drinking versus non-drinking was associated with a RR of 0.58 (95% CI 0.39, 0.87), suggesting a large protective effect. The highest category of beer consumers had an increased risk of dementia, with a RR of 1.84 (95% CI 1.01, 3.34); effects for all levels of spirits intake were not significantly different from those of non-drinkers (or the lowest drinking

category in each study). A striking feature was that all of the analyses, overall and by sub-groups, showed a very clear J-shaped curve for the relation of alcohol intake to dementia."

Weaknesses of the study included the fact that the authors were forced to use "current non-drinkers," or the lowest category of intake in each study, for the referent group, and could not separate ex-drinkers from life-time abstainers. In epidemiologic study analyses, if the referent group is defined only as "current non-drinkers" (without knowledge of previous drinking) this group will include a variable number of former heavy drinkers, who tend to have higher risk of many disease outcomes than do lifetime abstainers. If a large percentage of ex-drinkers were former heavy drinkers, this could make the risk of disease in the referent group high, and could over-estimate a protective effect seen among moderate drinkers. Where the percentage of former heavy drinkers in the current non-drinking group is small, there is generally little effect from including them with lifetime abstainers in the referent group.

The pattern of drinking could not be assessed in the present meta-analysis, so subjects who may have consumed relatively large amounts of alcohol on only one or two occasions each week (binge drinkers) could not be separated from regular moderate drinkers whose average *weekly* intake may have been similar. Also, there were no estimates or discussion of the potential impact on effect estimates of under-reporting of alcohol intake by subjects.

Forum member McEvoy stated: "I think the authors should have done more to qualify their findings of a greater beneficial effect of alcohol among younger than older adults. Many of the studies had relatively short follow-up periods, and a fairly young mean age or lower age range; thus these studies would not have captured dementia in their younger participants." Reviewer Van Velden thought that it was surprising that APOE 4 polymorphisms did not relate to the risk for neurodegenerative disorders in their analysis. Reviewer Samieri stated: "This meta-analysis is well-conducted and clearly concludes that the J-shaped curve applies to dementia risk, with more convincing associations found with wine compared to other alcoholic beverages (although, unfortunately, data on wine and dementia available in existing literature are inadequate to precisely investigate the dose-response relationship with wine)." Overall, Forum members considered this to be a very well-done analysis that strongly supports a J-shaped curve for the relation of alcohol consumption, especially of wine, to the risk of dementia.

<u>Are the protective effects on dementia only from wine?</u> Forum member Estruch noted: "I would like to underline the beneficial effects of wine on protection against cognitive decline and neurodegenerative disorders, as shown in this study. The only alcoholic beverage that was related to better cognitive function was wine; in fact, light to moderate wine consumption reduced by 42% the risk of developing dementia. The authors attributed this protective effect to resveratrol, but it is well known that other polyphenols in wine, such as anthocyanins (Kent et al), may play key roles in this effect." Reviewer Ellison noted the similar findings of Mehlig et al who, in a 34-year follow up for dementia among a cohort of Swedish women, found 40% or

greater reduction in the risk of dementia for wine drinkers, but a slight increase in risk for consumers of spirits.

Potential mechanisms for protection against dementia from wine consumption: Estruch suggested that, "Together with the anti-oxidant and anti-inflammatory effects of polyphenols in wine, we should also consider an attenuation of beta amyloid-mediated neuropathological mechanisms (Regitz et al)." In an extensive review of mechanisms, Forum member Stockley noted: "Data from animal studies suggest that grape- and wine-derived phenolic compounds are absorbed and accumulate in the brain in measurable amounts after multiple or repeated oral doses. Regarding potential mechanisms, the 'beneficial' effects of alcoholic beverages such as wine on both the risk of cardiovascular and cerebrovascular diseases have often been partly attributed to changes in lipid and hemostatic or blood flow factors. These changes include ethanol-induced increases in the concentration of high density lipoprotein-cholesterol; further, there are ethanol- and phenolic-induced increases in the thrombolytic proteins tissue-type plasminogen activator activity and tissue type plasminogen activator antigen, and induced reductions in fibrinogen and clotting cofactors factor VII and von Willebrand factor. These changes are also associated with a reduced risk of atherosclerosis which is the accumulation of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries."

Reviewer Stockley continued: "As atherosclerosis has been associated with both Alzheimer's disease and vascular dementia, it had been suggested that any beneficial effect of wine on atherosclerosis could be expected to benefit these dementias by preserving brain vasculature, consequently resulting in better cognitive function. Wright et al, however, showed that the appearance of plaque on the carotid artery which carries blood to the brain was not associated with consumption of an alcoholic beverage and associated improvements in cognitive function. This suggests then that ethanol and phenolic compounds such as resveratrol may impact cognition through a separate vascular or degenerative pathway (Kennedy et al). Further, vasoactive amyloid-β, associated with Alzheimer's disease and other related neurodegenerative diseases, may also interact with cerebral blood vessels to promote free radical production and reduce local blood flow changes, which precede other neuropathological changes in dementias, and subsequently upregulate amyloid-β production (Thomas et al). Indeed, among older persons without cerebrovascular and neurodegenerative diseases, those who moderately consume alcoholic beverages such as wine have been shown, in comparison with abstainers, to have fewer white-matter abnormalities and infarcts on magnetic resonance imaging (Mukamal et al). Also, pronounced reductions in the risk of both vascular dementia and Alzheimer's disease have been shown among persons consuming one to six standard alcoholic drinks per week (Moussa et al).

"Cognitive function is also associated with acetylcholine, and the ethanol component of alcoholic beverages may stimulate the release of acetylcholine in the hippocampus leading to

improved cognitive function, such that a light amount of an alcoholic beverage in normal subjects appears to improve memory for events experienced before consumption (Fadda et al). In contrast, the wine-derived phenolic compound, quercetin, inhibits acetylcholinesterase (Orhan et al).

"Yet another another potential therapy for Alzheimer's disease may involve preventing the aggregation of Aβ, as studies have suggested that only when aggregated in the fibrillar form Aβ is neurotoxic, although some studies alternatively suggest that the toxicity lies in soluble oligomeric intermediates rather than in the insoluble fibrils that accumulate. Resveratrol and its glucoside, piceid, have been shown in vitro to dose-dependently inhibit the formation of Aβ fibrils (Riviere et al, 2007, 2010)."

Forum member Mattivi also commented on potential mechanisms of effect: "The suggested additional protective effect of wine is here attributed to resveratrol, which is present in minor concentration in wine. It is well known that several phenolics are present in higher amount in wine (while absent or present at much lower concentration in the other alcoholic beverages considered in this meta-analysis). Some of these have the capacity to directly cross the blood-brain barrier (BBB). Among the compounds capable to cross the BBB, it is worth to mention the case of the anthocyanins (Fornasaro et al) and, in my opinion even more, of several microbial metabolites of polyphenols (Gasperotti et al). The most intriguing being possibly gallic acid, one of the major metabolites of red wine consumption, found at micromolar levels in the bloodstream. In animal studies (Gasperotti et al), gallic acid has been shown to have the brain as a main target. Gallic acid can accumulate in brain at concentrations six time higher than the plasmatic levels. Gallic acid is a metabolite capable to prevent the aggregation of beta amyloid . . . further studies on the putative mechanisms are definitely needed."

Reviewer Samieri added: "Regarding the phenolic compounds potentially responsible for the protective effects of wine on brain health, I would say existing literature is too limited to draw any conclusions on mechanisms of wine's effect on dementia risk. As Mattivi noted, anthocyanins and gallic acid may be interesting candidates. It may also be worth mentioning that quercetin metabolites (quercetin-3-O-glucuronide) can be detected in the brain of mice supplemented with moderate doses (equal to 2 glasses of wine per day in humans) of Cabernet sauvignon, and significantly reduced the generation of β-amyloid (Aβ) peptides by primary neuron cultures generated from the Tg2576 AD mouse model (Ho et al). It is also important to look at experimental studies in humans, because the metabolism is so different in humans compared to mice. In humans, flavanols from cocoa were able to increase neurovascular plasticity in the hippocampus and improve cognition (Brickman et al). Finally, a randomized, controlled, phase II trial was recently conducted with high-dose resveratrol in mild-to-moderate Alzheimer's Disease (AD) and demonstrated the ability of resveratrol to alter some AD biomarkers (Turner et al)."

Forum member De Gaetano described some work on this topic by his research team (Crescente et al). They evaluated resveratrol, quercetin, and gallic acid for their effects on platelets, and the interactions of these three different polyphenols among themselves and with aspirin, at the level of human platelet cyclooxygenase-1 (COX-1). Their analyses suggested that all three compounds form stable complexes in the COX-1 channel, with slightly different but functionally relevant interaction geometries. De Gaetano also noted that "Experiments in mice showed that gallic acid administered before aspirin, resveratrol or quercetin, fully prevented their inhibitory effect on serum TxB(2). Finally, a mixture of resveratrol, quercetin and gallic acid, at relative concentrations similar to those contained in most red wines, did not inhibit platelet aggregation, but potentiated sub-inhibitory concentrations of aspirin. Thus, gallic acid interactions with other polyphenols or aspirin at the level of platelet COX-1 might partly explain the complex, and possibly contrasting, effects of wine and other components of the Mediterranean diet on platelets and on the pharmacologic effect of low-dose aspirin."

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Forum Summary

A number of epidemiologic studies have found that light-to-moderate alcohol intake is associated with a lower risk of developing dementia and/or cognitive decline, while excessive drinking may increase the risk. The authors of the present paper carried out a meta-analysis of the current scientific literature that was based on data from 11 studies with 4,586 cases of all-cause dementia diagnosed among more than 70,000 subjects and two additional analyses of studies of approximately 50,000 subjects each for evaluating the association of alcohol intake with the diagnosis of Alzheimer's disease and for vascular dementia. Seven studies provided results according to type of alcohol consumed, while two provided results according to APOE 4 levels.

The conclusions of the authors are that light-to-moderate alcohol consumption was associated with lower risk of all types of dementia, with beverage-specific analyses indicating that the effect was primarily for wine. There was a suggestion of increased risk of dementia with heavy consumption of total alcohol. The presence or absence of APOE 4 did not appear to modify the effects. The authors state that the risk of dementia was lower for the overall consumption of alcohol of up to 12.5 g of alcohol/day (about one typical drink/day), and risk was increased for consumers of more than 38 g/day (about 3 to 4 typical drinks/day). However, essentially all of the protection against dementia occurred only among consumers of wine, rather than those consuming beer or spirits.

Forum reviewers considered this to be a very well-done meta-analysis of the current literature on the topic. It was based only on prospective epidemiologic studies of very good quality, and sub-analyses evaluated the separate effects of each type of alcoholic beverage. While the authors were unable to include the pattern of drinking (binge versus regular moderate) in their analyses, and could not test for previous alcohol consumption among current non-drinkers, Forum members agreed with the primary findings of a J-shaped curve between alcohol consumption and all types of dementia (including vascular dementia and Alzheimer's disease). The estimates of the authors were that, compared with non-drinkers, moderate consumers of wine showed a decrease of about 40% or more in the risk of dementia. Little effect was noted

among drinkers of spirits, and heavy beer drinkers appeared to have an increased risk of dementia.

Most of this Forum critique deals with potential mechanisms by which wine consumption may reduce the risk of dementia and/or cognitive decline. In addition to the effects of both alcohol and polyphenols in wine on decreasing atherosclerosis and having beneficial effects on hematological factors (affecting cerebral as well as coronary arteries), there may also be anti-inflammatory effects and direct effects on brain structures that play a role. Given that the beneficial effects seem to be primarily among wine consumers, and not for consumers of beer or spirits, this suggests that the polyphenols and other non-alcohol substances in wine (perhaps in interaction with alcohol) may be more important than the alcohol itself.

The mechanistic studies described in the paper and in this critique provide considerable support for the epidemiologic findings of less dementia and cognitive decline among moderate drinkers. Forum member agree with the authors of this paper that light-to-moderate wine consumption may help lower the risk of dementia, an increasingly important condition among the world's rapidly ageing population.

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Comments on this critique by the International Scientific Forum on Alcohol Research were provided by the following members:

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