Serum uric acid levels and multiple health outcomes

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Study question Which health outcomes are associated with serum uric acid levels and is the available evidence for the reported associations strong enough to indicate causality?

Methods In this umbrella review the authors systematically collected and evaluated evidence from systematic reviews and meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies. They identified 136 health outcomes that were examined in relation to serum uric acid levels across the three study types, including anthropometric outcomes, cardiovascular diseases, metabolic diseases, kidney disorders, various cancers, and neurocognitive diseases. To assess the credibility of the observed associations, the authors adopted a set of criteria. After assessment, no association from meta-analyses of observational studies was classified as convincing, and associations with five health outcomes (heart failure, hypertension, impaired fasting glucose or diabetes, chronic kidney disease, and coronary heart disease mortality) were classified as highly suggestive. Convincing evidence, indicating a causal effect of high serum uric acid levels, was found for only two outcomes: meta-analyses of randomised controlled trials for nephrolithiasis and Mendelian randomisation studies for gout.

Study flowchart

What this study adds

This comprehensive umbrella review will help investigators to judge the relative priority of health outcomes related to serum uric acid level for future research and clinical management of disease.

Funding, competing interests, data sharing

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**Alcohol consumption and brain health**

**ORIGINAL RESEARCH** Longitudinal cohort study

**Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline**

Topiwala A, Allan C L, Valkanova V, et al

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**Study question** Does moderate alcohol consumption have a favourable or adverse association or no association with brain structure and function?

**Methods** Participants (n=550) were adults (mean age 43.0 (SD 5.4) at study baseline) who were living in the community and were enrolled in the Whitehall II cohort. Weekly alcohol intake and cognitive performance was measured repeatedly during a 30 year period (1985-2015). Multimodal magnetic resonance imaging (MRI) was performed at study endpoint (2012-15). Outcomes were structural neuroimaging measures and cognitive decline.

**Study answer and limitations** 20.0% of men and 13.6% of women drank in excess of contemporaneous (pre-2016) UK guidelines (<21 units and <14 units weekly respectively) on average across the study. Higher alcohol consumption over the 30 year follow-up was associated with increased odds of hippocampal atrophy. While those consuming over 30 units a week were at the highest risk compared with abstainers (odds ratio 5.8, 95% confidence interval 1.8 to 18.6; P≤0.001), even those drinking moderately (14-21 units/week) had three times the odds of right sided hippocampal atrophy (3.4, 1.4 to 8.1; P=0.007). There was no protective effect of light drinking (1-<7 units/week) over abstinence. Higher consumption was additionally associated with poorer white matter integrity and faster cognitive decline on lexical fluency, such that those drinking 7-<14 units weekly experienced 14% greater reduction in performance from their baseline over 30 years than abstainers (P=0.015). This was an observational study and participants might not be representative of the wider population. As the MRI was performed on a single occasion at the end of study, we cannot exclude reverse causation—that is, those with hippocampal atrophy at study baseline were more likely to drink more.

**What this study adds** There is a dose dependent association between alcohol consumption and hippocampal atrophy. Light drinking does not seem to have a protective effect over abstinence on brain structure or function.

**COMMENTARY** Even moderate drinking is linked to pathological changes in the brain

Epidemiological studies often report better health in moderate drinkers compared with abstainers. Observed first in studies of incidence of myocardial infarction, the “J shaped curve” (describing the graphical appearance of health measures plotted against consumption) reappears in studies of diabetes, stroke, and even chronic widespread pain. As methods of investigating the association between alcohol and health are refined, however, the size of the apparent benefits reduces substantially.

Studies using “Mendelian randomisation,” purportedly impervious to confounding or reverse causality, do not support the original claim that moderate drinking improves cardiovascular health. Regarded as a further example of the J shaped curve, a protective effect of moderate alcohol consumption against “all cause” dementia has been reported. This has not been underpinned by a convincing neural correlate, however, and it is here that the linked study by Topiwala and colleagues’ findings strengthen the argument that drinking habits many regard as normal have adverse consequences for health by Topiwala and colleagues is particularly ambitious. In their prospective cohort of 550 civil servants, none of whom were alcohol dependent, the authors repeatedly assessed alcohol consumption and cognition over 30 years. Participants underwent brain imaging at the most recent review, enabling examination of relations between average alcohol use, cognition, and brain structure.

**Dose dependence**

After adjustment for numerous potential confounders, alcohol use was associated with reduced right hippocampal volume in a dose dependent manner; even moderate drinkers (classified as up to 21 units a week for men at the time of the study) were three times more likely to have hippocampal atrophy.
than abstainers, and very light drinking (1-6 units a week) conferred no protection relative to abstinence. Higher alcohol consumption was also associated with reduced white matter integrity and faster decline in lexical fluency, a test of “executive function.”

With increasing longevity, maintenance of brain health into older age is the key priority of our time. Leaving aside the human cost of dementia, care of cognitively impaired older people is a looming financial crisis, prompting politicians to consider controversial and deeply unpopular policy decisions. Alcohol dependence is already established as a major cause of dementia, alcohol related brain damage (ARBD) accounts for possibly 10% of early onset dementia and potentially 10-24% of dementia cases in nursing homes.

Existing on a spectrum of severity, alcohol related brain damage typically involves relatively young people, often in their 40s or 50s, meaning the more severely affected require decades of institutional care. While alcohol related brain damage generally afflicts malnourished drinkers consuming very high levels of alcohol, some degree of potentially reversible cognitive impairment is detectable in most people starting treatment for alcohol dependence. Alcohol can be the primary cause of cognitive impairment in some individuals, but it is a likely contributor to cognitive decline in many more.

The chief medical officer recently changed guidance for low risk drinking in men, reducing the recommended maximum intake from 21 to 14 units a week. This was because of accumulating evidence that even light drinking increases the risk of various malignancies. The relation between alcohol and brain health is more complex than the relation between alcohol and cancer. While there is almost universal agreement that heavy drinking is associated with cognitive impairment, numerous observational studies do report that light to moderate consumption is associated with a reduced risk of all cause dementia.

**Abstinence is best**

While concerns about confounding and inconsistencies between studies make it difficult to define what level of intake is “optimal” for cognition, it seems to be low; in these studies around a unit a day is associated with the lowest risk of dementia, with risk for drinkers clearly exceeding abstainers by 4 units a day. Topiwala and colleagues’ report of adverse effects at even lower levels of intake, coupled with the finding that drinking more than 14 units a week was associated with both brain pathology and cognitive decline, provides further support for the chief medical officer’s recent decision.

How should this paper inform discussions with patients? It certainly strengthens the view that if alcohol does confer beneficial effects on health, the link is probably confined to low intakes of no more than a unit a day. Even this level of consumption carries risk relative to abstinence for conditions such as breast cancer, and the evidence of benefit is certainly not strong enough to justify advising abstainers to drink.

As intake increases, so does the risk to health, probably in a dose dependent manner. Heavy consumption is associated with potentially severe impairments in memory and executive function, even when other obvious risk factors are absent. Topiwala and colleagues’ findings strengthen the argument that drinking habits many regard as normal have adverse consequences for health. This is important. We all use rationalisations to justify persistence with behaviours not in our long term interest. With publication of this paper, justification of “moderate” drinking on the grounds of brain health becomes a little harder.

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Results of voxel based morphometry (corrected for threshold-free cluster enhancement (TFCE)): significant negative correlation between weekly alcohol units (average of all phases across study) and grey matter density in 527 participants. Adjusted for age, sex, education, premorbid IQ, social class, physical exercise, club attendance, social activity, Framingham stroke risk score, psychotropic drugs, and history of major depressive disorder.
Evolution of poor reporting and inadequate methods over time in 20,920 randomised controlled trials included in Cochrane reviews

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Study question How have poor reporting and inadequate methods for key methodological features in randomised controlled trials (RCTs) changed over the past three decades?

Methods The authors mapped 20,920 RCTs included in 2001 Cochrane reviews published between March 2011 and September 2014. For each RCT, the consensus on risk of bias made by the review authors was extracted for sequence generation, allocation concealment, blinding, and incomplete outcome data. The primary reference was identified to extract publication year and journal. Journal names were matched with Journal Citation Reports to get 2014 impact factors. The proportion of trials considered by the review authors at unclear and high risk of bias were used as surrogates for poor reporting and inadequate methods, respectively.

Study answer and limitations 48.7% of trials were at unclear risk of bias for sequence generation and 57.5% for allocation concealment; 4.0% and 7.2% were at high risk, respectively. For blinding and incomplete outcome data, 30.6% and 24.7% of trials were at unclear risk and 33.1% and 17.1% were at high risk, respectively. Higher journal impact factor was associated with a lower proportion of trials at unclear or high risk of bias. The proportion of trials at unclear risk of bias decreased over time, especially for sequence generation, which fell from 69.1% in 1986-90 to 31.2% in 2011-14 and for allocation concealment (70.1% to 44.6%). After excluding trials at unclear risk of bias, use of inadequate methods also decreased over time: from 14.8% to 4.6% for sequence generation and from 32.7% to 11.6% for allocation concealment. This study relied on Cochrane reviewers’ assessment of risk of bias, which could be variable.

What this study adds We took advantage of the amount and quality of data included in Cochrane reviews to map the evolution of poor reporting and inadequate methods within and across journals. Our results show a decrease over time of poor reporting and inadequate methods especially for sequence generation and allocation concealment. We found a lower proportion of RCTs with poor reporting and inadequate methods in journals with higher impact factors. By contrast, our results raise concerns about journals with no or low impact factors because of the prevalence of poor reporting and inadequate methods.