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JOURNAL CLUB

Population studies highlight an increased risk of dementia in both dependent and non-dependent drinkers

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Introduction

Alcohol use is widespread and increasing in the developing world. Recent evidence highlighting the association of alcohol with an increased risk of cancer has prompted revision of some national consumption guidance. However, excess alcohol consumption is often accompanied by adverse socioeconomic factors, making its association with healthcare outcomes complex and difficult to interpret.

Prior studies exploring links between alcohol and dementia have mostly involved cross-sectional and/or short-term prospective data and focussed principally on the effects of heavy alcohol intake mediated through thiamine deficiency. Evidence for longer term morbidity in non-dependent drinkers is less robust. As a result, although a few studies have demonstrated an association between alcohol and dementia, alcohol use is absent from the modifiable risk factors included in the "Dementia Prevention, Intervention, and Care" report commissioned by The Lancet in 2017. Indeed, some previous research has suggested a beneficial effect of light alcohol consumption on brain outcomes.

The three papers in this month's journal club describe a series of large-scale population-based studies examining the association of alcohol with neuroimaging and neurocognitive markers of dementia, as well as clinical outcomes. The inclusion of mild and moderate drinkers as well as more heavy drinkers yields insights into the dose-dependent effects of alcohol on the brain.

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Moderate alcohol consumption as a risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study

This study comprised a large observational cohort study of 550 patients [mean age 43.0 (SD 5.4) at study baseline] who had been enrolled onto the Whitehall II study, taking place over 30 years. Longitudinal alcohol history was taken at different interviews across the 30 year period; comprising units drunk per week, frequency of drinking a week over a year, and the 'CAGE' questionnaire. Participants were split into 6 groups based on weekly average alcohol consumption across the 30 year period. A variety of sociodemographic factors were controlled for.

Brain scans were performed at the end of the study period, with magnetic resonance imaging as well as diffusion tensor imaging. Grey matter density, white matter microstructure and hippocampal volume (using visual rating scales and grey matter density estimations) were analysed. In addition, longitudinal cognitive testing as well as detailed cross-sectional cognitive testing (at the time of scanning) was performed.

The authors found higher average weekly alcohol consumption was negatively associated with grey matter density, especially in hippocampal regions. Increased alcohol intake was also associated with higher rated atrophy on visual rating scales. Although most pronounced in those drinking above 30 units (odds ratio 5.8, 95% confidence interval 1.8–18.6; $P \leq 0.001$), this was also seen for those drinking between 7 and 14 units (3.4, 1.4–8.1; $P = 0.007$). There was no protective effect of light drinking (1–7 units/week) over abstinence. Higher alcohol consumption was associated with worsening white matter integrity with lower corpus callosum fractional anisotropy as well as higher radial, axial, and mean diffusivity.

Higher alcohol consumption was associated with faster decline on lexical fluency scores over the testing period; 14% decline in drinkers of 7–14 units per week; 17% decline

in those drinking 14–21 units per week; and 16% decline in those drinking more than 21 units per week. The same results were not replicated for longitudinal tests of semantic fluency or short-term memory, nor the cross-sectional detailed neurocognitive battery performed at the time of imaging.

Comment. This study combined longitudinal alcohol history with modern imaging measures and both cross-sectional and longitudinal cognitive testing. The authors have controlled for a variety of factors which might contribute to cognitive dysfunction, and suggest that alcohol's effects on the brain extend even into what are currently considered 'moderate' levels of consumption (7–14 units per week).

A clinical diagnosis of dementia was not one of the outcome measures studied. Although hippocampal atrophy and reduced lexical fluency are markers of Alzheimer's type disease process, similar changes in other cognitive domains were not associated with increasing alcohol intake (perhaps due to insufficient follow up or patients being at pre-clinical stage). There is a discrepancy between the risk of developing right-sided hippocampal atrophy (significant at > 14 units a week) and left-sided atrophy (only significant at > 30 units a week), which future studies should address. Although we have evidence for decline in lexical fluency over time, we do not have longitudinal data for the brain imaging and detailed neurocognitive assessment, which potentially could also have changed over the study period.

The sample itself was a particularly male-dominated one, explaining why some of the results were not significant for female participants. The sample being all middle-aged civil servants also did not perhaps offer a true representative real-life population. In addition, we do not have information on the early life drinking habits prior to middle age, perhaps missing relevant early life drinking behaviours and underestimating their effect.

Topiwala A et al (2017) BMJ 6;357: j2353.

Contribution of alcohol use disorders to the burden of dementia in France 2008–2013: a nationwide retrospective cohort study

This French nationwide retrospective cohort study recorded data from the French national database for all adults over 20 admitted to hospital over a 5-year period. Associations of alcohol use and a dementia diagnosis were analysed for all patients admitted from 2008 to 2013 (with no record of dementia in 2008–2010). Dementia subtypes were defined as alcohol related, vascular, and other (including Alzheimer's disease). Alcohol use disorders were defined by mental and behavioural disorders due to former or current chronic harmful use of alcohol (including alcohol abstinence), alcoholic liver disease, Wernicke–Korsakoff's syndrome, end-stage liver disease/other forms of cirrhosis, epilepsy, and head injury.

Of 31,624,156 discharged pts 945,512 (3.1%) had alcohol use disorders; meanwhile, 1,109,343 (4.2%) had a diagnosis of dementia. 57,353 (5.2%) of dementia patients were defined as early onset dementia (onset before age 65). 38.9% of these early onset dementias were labelled as 'alcohol related', and 17.6% of the early onset dementia patients had an additional diagnosis of an alcohol use disorder.

The association between young onset dementia and alcohol remained robust even when controlling for other associated factors for heavy alcohol consumption and dementia, such as smoking, hypertension, and obesity. Although 64.9% of all dementia cases were women, the majority (again 64.9%) of early onset dementia patients were men. Alcohol use disorders were the strongest modifiable risk factor for dementia onset, with an adjusted hazard ratio of 3·34 (95% CI 3·28–3·41) for women and 3·36 (3·31–3·41) for men. In addition, alcohol use disorders were significantly associated with all other risk factors for dementia onset (all $p < 0{\cdot}0001$). Although alcohol abstinence was associated with lower risk of competing mortality over the lifespan, there was no reduction in the risk of developing dementia.

Comment. This study suggests that the burden of dementia due to alcohol is much larger than previously thought, and that the majority of young onset dementia patients had an associated alcohol use disorder. The researchers also suggest that alcohol can exert lifelong brain damage, as those who abstained, but previously drank, did not have a reduced risk of dementia (although there was limited information on early life drinking patterns). The results are likely to be representative as over 80% of the French population over 65 years were admitted to hospital at some point during the study period and included in the analysis. However, generalising these results across the developed world requires caution, as there are considerable differences in average per capita alcohol consumption.

Care also needs to be taken when interpreting data from large-scale data-inputting sources due to risk of incorrect entry and some lack of information about the diagnosis of dementia, including neuroimaging or neuropathological correlates. A subgroup analysis of specific diagnoses such as Alzheimer's disease, Frontotemporal dementia, or diffuse Lewy body disease may be useful for future studies.

Schwarzinger M et al (2018) Lancet Public Health 3(3): e124-e132.

Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway

This was a large retrospective population-based study in Norway exploring at the links between self-reported alcohol consumption and the risk of dementia up to 27 years later. 88% of the population of the Norwegian county of Nord-Trøndelag had been recruited into the Nord-Trøndelag Health Study (HUNT) between 1984 and 1986. The current study selected participants from HUNT who were born between 1905 and 1946 (average age 58). Participants completed two questionnaires on the frequency of alcohol consumption. During HUNT participants also underwent medical examinations (such as measurement of blood pressure, height, and weight).

To confirm dementia diagnoses, between 2008 and 2010 patient files from the memory clinics at the two hospitals in Nord-Trøndelag were examined by experts in old age psychiatry and geriatric medicine. In addition, from 2010 to 2011, nursing home residents in Nord-Trøndelag were invited to participate in an extensive health examination, with trained nurses using standard interviews to record those with a diagnosis of dementia. Results were adjusted for age, sex, years of education, hypertension, obesity, smoking, and symptoms of depression.

Of 40,435 individuals, 1084 participants had a diagnosis of dementia. When adjusting for age and sex, compared to infrequent drinkers (1–4 times per 2 weeks), alcohol abstainers and frequent drinkers (> 5 times per 2 weeks) were at a higher risk of developing dementia, with hazard ratios of 1.30 (95% CI 1.05–1.61) and 1.45 (1.11–1.90), respectively. In the fully adjusted analysis, however, it was only the frequent drinkers with an increased dementia risk, with a hazard ratio of 1.40 (1.07–1.84). When results were broken down, equivalent results for Alzheimer's disease and vascular dementia indicated the same patterns of associations, albeit these were individually not significant.

Comment. This study used available data on alcohol consumption to suggest that more frequent drinking is associated with a higher risk of developing dementia decades later. The authors did not find that infrequent alcohol consumption was associated with reduced dementia risk compared to abstaining. The study used a large representative sample and a long observation period (up to 27 years) in which participants may have acquired a clinically validated diagnosis of dementia.

Only patients born between 1905 and 1946 were included, meaning early life drinking patterns are lacking, along with some early onset dementia diagnoses. The rate of dementia was also likely under reported, as the memory clinics only contained diagnoses of dementia between 1998 and 2010. Unfortunately, a large number of participants (22,210) died through the observation period. We do not know specifically whether dementia or alcohol related complications contributed to their death.

The alcohol assessment tool used only included frequency of drinking, and not volumes consumed, type of alcohol consumed, binge drinking tendencies, or early life drinking habits. The study did not differentiate between heavy drinkers, as all drinkers of 5 times or above in 2 weeks were grouped together as heavy drinkers. Overall relatively few participants (6.5%) were classed as heavy drinkers, which is below the Norwegian average, and suggests a degree of under reporting of alcohol intake.

Langballe E et al (2015) Eur J Epidemiol 30:1049–1056.

Conclusions

These studies provide evidence for a dose-dependent correlation of alcohol intake with dementia. The longitudinal follow up data suggest that the effects of excessive alcohol consumption may only be manifest many years later. Importantly, there is evidence that mild-to-moderate drinkers are at a significantly increased risk of dementia as well as heavy drinkers, and that there is no clear evidence for the beneficial effect of light alcohol consumption.

It may be difficult to draw cause and effect from such observational studies, but they have generally controlled effectively for co-morbidities and confounding factors, and drinking behaviour predates dementia-related outcomes by decades in these studies. We must acknowledge that there is a lack of standardisation in definitions and descriptions of alcohol consumption, as well as dementia outcome measures, making direct comparisons between studies difficult.

Further research should focus on drinking habits around the world, given that health risks associated with alcohol consumption can vary between countries. More work also needs to be conducted on the specific neurobiological effects of alcohol excess, as well as into neuroimaging characteristics. Analysis of early life drinking patterns, established patterns of drinking, specific effects of binge drinking, as well as the types of alcohol consumed is much needed.

These three studies seem to suggest even the revised current guidelines are insufficient in protecting us from the neurotoxic effect of alcohol on the brain. As a sobering thought, next time we are at the bar, do we really know the true meaning behind the question "what's your poison?"