Effects of drinking on late-life brain and cognition

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ABSTRACT

Alcohol consumption is common in Western countries and has been increasing in older adults. Latest figures from Great Britain suggest 75% of those over 65 years drink, an increase from 71% 10 years ago. Chronic heavy intake is a well-established cause of brain atrophy and dementia, with a recent long-term prospective study from the USA reporting a doubling of the odds of later severe memory impairment in those with a history of an alcohol use disorder. Drinking of moderate amounts has been reported to be protective for brain health in a number of epidemiological studies, including some claims of possibly reducing dementia risk. Rigorous recent research has questioned this belief, with new evidence of harmful associations in moderate drinkers compared with abstainers. This has raised suspicion that reported protective effects of moderate drinking were due to confounding by socioeconomic class and intelligence. Clinicians should look out for cognitive impairment in heavy drinkers, considering that abstinence may induce a degree of clinical improvement. Discussions with patients regarding moderate drinking should be informed by recent research. Health benefits of moderate drinking at least for cognitive function are questionable, and if they exist are probably limited to one unit of alcohol daily with respect to other body systems.

INTRODUCTION

Alcohol use is widespread and increasing across the developed world. Latest figures suggest that 58% of the UK population is drinking in excess of existing safe limits,[1] with 5% men and 4% of women consuming hazardous amounts (>50 units (400 g) for men and >35 units (280 g) for women weekly). Drinking in women and older adults of both sexes has been increasing,[2] with the percentage of those >65 years drinking increasing from 71% to 75% between 2005 and 2016. Those over 65 years of age are now more likely than any other age group to have drunk on at least 5 days in the preceding week.[1] Alcohol-related harm is estimated to cost England around £21 billion per year, with £3.5 billion to the NHS, £11 billion tackling alcohol-related crime and £7.3 billion from lost work days and productivity costs. Health concerns associated with alcohol use have focused on liver dysfunction and more recently cancer. The public are largely ignorant of the potential risks of drinking with regards to cognition, in contrast to widespread knowledge of effects on the liver.[3] Recommended drinking guidelines have remained unchanged in the UK from 1987 until 2016. Safe limits for men were set at 21 units (168 g) and for women at 14 units (112 g) per week pre-2016. Recent evidence of associations with cancer risk[4] at lower doses prompted revision of UK government alcohol guidance to 14 units (112 g) for both sexes, but current US guidelines still suggest that up to 24.5 units (196 g) weekly is safe for men.

This clinical review summarises established effects of chronic heavy drinking on brain and behaviour/cognitive function, as well as the poorly understood impact of moderate consumption. Implications for clinicians from these findings are also discussed.

METHODS

MEDLINE, PubMed and Google Scholar were searched with the following keywordskeywords: 'alcohol' AND ('dementia' OR 'cognition' OR 'brain'). Primary research and review articles published in English until 10 September 2017 were examined for information pertinent to the topic. Reference lists from included papers were hand searched for additional relevant articles.

RESULTS

Our search retrieved a large consistent evidence base to suggest an increased risk of dementia and cognitive impairment, and brain atrophy in the context of chronic heavy alcohol consumption. In contrast, data pertaining to risks or benefits of lesser intakes were conflicting, perhaps in part because definitions of 'moderate' consumption varied considerably. In this review we focus on five epidemiological studies and two meta-analyses pertaining to the risk of dementia with moderate alcohol use, five studies and two meta-analyses investigating the risk of cognitive impairment, and nine studies examining neuroimaging outcome measures. Table 1 gives a summary of the main findings.

Overall, acute intoxication with alcohol results in behavioural disinhibition, disrupted socioemotional processing and impaired psychomotor performance. The molecular basis for these actions is thought to include NMDA and GABA-A receptors. High doses of alcohol acutely reduce prefrontal and temporal lobe function, including planning, verbal fluency, memory and complex motor control including cerebellar function.[5] The pattern of impairment has been compared with that seen in hippocampal damage. Excessive alcohol consumption can also lead to a number of conditions with psychiatric symptoms, including psychotic disorders and delirium. In this review we focus on structural brain and cognitive sequelae of chronic alcohol consumption.

Chronic heavy alcohol

Cognitive sequelae

Chronic heavy drinking is associated with a number of serious neurological conditions, one of which is Wernicke's encephalopathy. This is an acute, often lethal, but potentially reversible neurological disorder caused by a severe deficit in thiamine (vitamin B1) aggravated by carbohydrate overload. It is characterised by the clinical triad of oculomotor disturbance, cerebellar dysfunction and altered mental state. Chronic alcohol users are at risk of this due to multiple potential factors including: poor diet, impaired absorption and altered metabolism of thiamine. The estimated mortality of Wernicke's encephalopathy is 17%. Untreated, 80% of survivors of Wernicke's encephalopathy will progress to the severe and usually permanent Korsakoff's syndrome.[6] This is characterised by anterograde (and retrograde) amnesia, and frequently occurs together with prefrontal deficits. Even in 'uncomplicated' alcoholism, without Wernicke's encephalopathy or Korsakoff's syndrome, over 80% of individuals have executive deficits,[7] although of a lesser severity. A strong evidence base supports the association of heavy alcohol consumption over long periods with increased dementia risk and cognitive decline.[8] A recent long-term prospective study from the USA reported that individuals with a history of an alcohol use disorder have more than double the odds of later severe memory impairment compared with controls (OR 2.21, 95% CI 1.27 to 3.85).[9] There is some debate as to whether primary alcohol dementia exists, as a result of direct neurotoxicity, or whether

Table 1 Summary of associations between alcohol consumption, cognition and brain structure.

Outcome	Chronic heavy intake	Moderate intake
Cognitive outcomes		
Dementia risk	Consistently increased[11]	Conflicting results, with some studies reporting a protective effect[26 28 31] which others have failed to replicate[29 30]
Cognitive decline	Consistently increased[8 9]	Conflicting results, with some studies reporting a protective effect[34 35] which others have failed to replicate[32 36 37 46]
Brain structure		
Grey matter	Widespread atrophy, especially of frontal lobes[12]	Two studies reported atrophy[40 41] but others have not[39 42]
White matter	Widespread atrophy, including of frontal lobes, cerebellum and corpus callosum[13 20]	Two studies have found negative associations[44–46] and others have not[43]
Subcortical volumes	Hippocampi,[51] amygdalae,[16] mammillary bodies, hypothalamic and thalamic nuclei all potentially affected[52]	Two studies report conflicting associations with hippocampal size[43 46]
Cerebellum	Atrophy[17]	Insufficient evidence

cognitive deficits are entirely secondary to an additional pathology, for example, due to thiamine deficiency. It is difficult to disentangle these possibilities, particularly in view of multiple confounders in dependent drinkers, such as smoking, comorbid substance abuse and increased vascular risk. Similarly, establishing the prevalence of alcohol-related dementia is difficult, due to a lack of operationally defined diagnostic criteria. Estimates differ from 9% to 22% of all patients with dementia,[10] or even higher in nursing homes. Dementia of alcoholic aetiology may be particularly prevalent in earlier-onset dementia. There is no clear answer, as to what level of consumption is sufficient to cause Korsakoff's syndrome. Oslin *et al*[11] have suggested a 5-year intake greater than 35 units (280 g) weekly for men and 28 units (224 g) for women, but this needs validation. Thresholds are likely to be different according to sex, comorbid conditions and genetic susceptibility.

Effects on brain structure

Brain atrophy in chronic alcoholism is well described.[12] The frontal lobes are thought to be particularly vulnerable. Kril *et al* found frontal cortex reductions of 23% in uncomplicated alcoholism, replicating earlier findings. MRI studies have also reported widespread cortical atrophy, which may particularly affect the frontal lobes.[13] Interestingly, longitudinal MRI has shown a degree of tissue recovery, especially of white matter, on abstinence.[14]

The hippocampus is consistently affected in animal models of chronic alcoholism. Despite the preclinical data, evidence for hippocampal involvement in humans is less convincing. However, Bengochea and Gonzalo, among others, have described hippocampal loss in individuals with chronic alcoholism compared with controls.[15] Reduced amygdala volume has also been described in those with lifelong high alcohol consumption (defined as >80 g daily for the majority of their adult lives), and including those with Wernicke-Korsakoff's syndrome.[16] The cerebellum, known for its importance in motor function, is now additionally thought to play a role in memory disturbance.[17] A number of neuropathological studies have established cerebellar atrophy in chronic alcohol abuse.[18] Mammillary body atrophy is almost universal in chronic alcoholism. However, animal studies suggest that other hypothalamic nuclei, particularly the supraoptic and paraventricular, may also be affected.[19] Anterior thalamic nuclei may be affected in humans.

Several preclinical and postmortem studies have provided evidence of prominent white matter loss following chronic heavy alcohol use, which may exceed grey matter loss.[20] The frontal lobes and cerebellum are particularly vulnerable. Furthermore, white matter loss in the temporal lobes has been linked to alcohol withdrawal seizures.[21] The corpus callosum, a major commissural tract, may be particularly vulnerable. In their postmortem study, Harper and Kril reported that corpus callosum thickness in a group of alcoholics (3.19 mm) was significantly reduced compared with controls (4.02 mm).

A number of different mechanisms have been proposed to account for the deleterious effects of chronically high alcohol consumption on the brain. Damage to the brain from chronically high levels of alcohol is thought to result, at least in part, from thiamine deficiency. Deficiency of thiamine has been linked to oxidative stress, excitotoxicity, inflammatory responses, dysfunction of the blood-brain barrier and lactic acidosis. Ethanol could also be directly neurotoxic. Alcohol inhibits glutamate receptors. Chronic exposure induces upregulation of NMDA receptors, which leaves neurons vulnerable to excitotoxicity from massive calcium influx. This may be driven especially by repeated binges and withdrawal. Cell death could also be via neuroinflammation, the induction of inflammatory mediators and microglia.[22] Additionally, alcohol-related liver dysfunction could mean that neurotoxic substances such as ammonia and manganese are not removed from the blood, resulting in cerebral effects.

Moderate chronic alcohol use

There is no universal agreement about the definition of 'light' or 'moderate' drinking. Moderate drinking is defined variably in the literature from 9 units to 18 units (72–144 g) weekly.[23 24] In contrast to heavy consumption, the long-term effects of moderate alcohol consumption on cognition are poorly understood. A J-shaped relationship of cognitive function with alcohol use has been suggested, similar to that with cardiovascular disease, that is, small amounts of alcohol are associated with a reduced risk than abstinence, but large amounts with the greatest risk. Ethanol's inhibition of platelet aggregation, reduction in inflammatory markers and alteration of plasma lipid profile have been proposed as underlying mechanisms for protection from cardiovascular disease, in addition to the antioxidant action of polyphenols present in some alcoholic drinks.[25]

Risk of dementia

Several large epidemiological studies have reported a reduced risk of dementia (of vascular and non-vascular aetiology) in light drinkers to moderate drinkers compared with abstainers. For example, Ruitenberg *et al* found those drinking one to three drinks (14–46 g) per day had a reduced risk of dementia (HR 0.58, 95% CI 0.38 to 0.9) compared with abstainers in the Rotterdam Study.[26] Subjects were over 55 years old at baseline, and followed up for an average of 6 years. Dementia was excluded at baseline using a variety of screening tests, such as the Mini-Mental State Examination (MMSE), Geriatric Mental State (GMS) and Cambridge Cognitive Examination (CAMCOG). In the French prospective PAQUID Study, individuals who were at least 65 years old at baseline were followed up for 3 years. Both 'light' wine drinkers (<1–2 drinks

(14–32 g) daily) and 'moderate' wine drinkers (3–4 drinks (46–64 g) daily) had reduced odds of incident Alzheimer's disease.[27] Similarly, Mukamal *et al*[28] reported a lower dementia risk in those drinking one to six drinks (14–84 g) per day in the Cardiovascular Health Study, using a nested case-control design. Those thought to have dementia were excluded at baseline. A large Norwegian longitudinal study reported increased dementia-related deaths in moderate drinkers compared with abstainers.[29] However, others have not replicated these findings, including a recent study in an Australian cohort, which found no association with incident dementia or cognitive decline, and no interaction between alcohol and the ApoE4 genotype.[30]

Meta-analyses of such studies have cited a protective effect of light to moderate alcohol consumption on the risk of dementia including Alzheimer's disease.[31–33] Anstey *et al* analysed 15 prospective studies and reported a pooled risk reduction of 25%–8% with late-life drinking. They cautioned however that it was unclear whether this represented selection bias, that is, those still drinking in late life were likely to be those *without* dementia, or a genuine protective effect.

Risk of cognitive impairment or decline

In a large study of women in the USA, the Nurses Health Study, Stampfer *et al*[34] followed up women aged 30–55 years at baseline, using a cognitive test modelled on MMSE and later with a verbal recall task. Those consuming one drink daily had better cognitive scores than non-drinkers at baseline, and less cognitive decline at 2-year follow-up. The analysis was controlled for age, education level, social integration and cardiovascular risk factors. In another US study, Ganguli *et al*[35] followed up individuals aged at least 65 years at baseline for 2 years on a range of cognitive tests, including MMSE, Trail Making Test word recall and category fluency. Both minimal (defined as <1 drink (14 g) monthly) and moderate (<1 drink (14 g) daily) drinkers displayed less decline on MMSE and traits tests compared with abstainers. Interestingly, the protective effects were more pronounced when the comparison group of abstainers also included former drinkers rather than only lifelong abstainers.

However, not all studies have replicated a protective effect of light drinking on cognition. Lobo *et al*[36] did not find less MMSE decline in light drinkers than in abstainers. Bos *et al*[37] recently reported increased risk of cognitive decline (non Alzheimer types) with increased alcohol. Others have found a protective effect of moderate alcohol use only in those not carrying the ApoE4 allele (a risk gene for late-onset Alzheimer's disease).[38]

Meta-analyses have been limited by the paucity of studies. Peters *et al*[32] found no protective effect of moderate alcohol consumption on cognitive decline. Similarly, Anstey *et al*[31] found no significant effect of alcohol consumption on cognitive decline, but their analysis was limited to two studies and consequently had a high degree of heterogeneity.

Brain correlates

No convincing neural correlate for a protective effect of small amounts of alcohol on human brain structure has been found, although the field is poorly studied. Reported results are inconsistent.[39] Moderate alcohol consumption in older subjects has been associated with reduced total brain volume, increased ventricle size,[40] grey matter atrophy[41] and reduced frontal and parietal grey matter density, but others have not found such relationships,[39] or only at higher consumption levels.[42] Associations between moderate alcohol consumption and white matter findings are also inconsistent. De Bruin reported increased white matter volume in moderate drinkers compared with abstainers,[43] whereas Anstey found the inverse relationship.[44] Similarly, increased white matter hyperintensities have been described in moderate drinkers compared with abstainers[45] but others found no association.

In a cohort of 550 adults, we examined structural neuroimaging outcomes and cognitive decline in relation to alcohol consumption over the preceding 30 years. We found a novel dose-dependent association between alcohol intake and hippocampal atrophy. Just 14–21 units (112–168 g) of alcohol weekly was associated with almost three times odds of hippocampal atrophy compared with abstinence.[46] Additionally, alcohol consumption in non-dependent drinkers was associated with lower white matter integrity, particularly of the corpus callosum, and faster cognitive decline on lexical fluency, a complex executive task necessitating generation of words beginning with a specific letter within a time limit. Interestingly, we did not find moderate drinkers declining faster on semantic fluency (generation of words within a specific category) or memory recall, especially surprising given the hippocampal associations. Two possible explanations we can think of are that there are greater practice effects for semantic memory that were inadequately controlled for (despite best efforts), or that hippocampal atrophy represents an intermediate phenotype, similarly to in Alzheimer's disease, and cognitive symptoms were not yet evident at the last testing point in the study.

DISCUSSION

How can the seemingly contradictory epidemiological protective claims be explained given the recent harmful brain associations of moderate drinking? One explanation is confounding. Moderate alcohol consumption is highly allied to socioeconomic status and education.[1] Therefore characteristics that predict higher performance on cognitive testing, or a later diagnosis of dementia, are also associated with a likelihood of alcohol consumption. One method to try to obviate the problems of residual confounding is the use of Mendelian randomisation.[47] This technique is akin to a randomised controlled drug trial, except instead of a medication being randomly allocated to individuals, genetic variants are the instrumental variable, allocated at meiosis. Alcohol metabolism genes, for example, ADH or ALDH, explain some of the variance of consumption and have been used to investigate associations with cognition or dementia. Two studies thus far have attempted to apply this technique to the question of moderate alcohol and cognition. Almeida *et al* found no protective effect of moderate drinking on cognitive decline (defined as MMSE <23/30) over a 6-year period in older men.[48] Nor did Yeung *et al*[47] find a protective association with cross-sectional performance on MMSE and word recall using Mendelian randomisation of the ALDH2 genotype in the Guangzhou Biobank. However, both these studies may have been underpowered.

CLINICAL IMPLICATIONS

Identification of patients drinking large amounts of alcohol over a long period is important given the high risk of cognitive impairment and dementia, particularly as abstinence may improve symptoms to some degree. Screening instruments, such as CAGE or the Alcohol Use Disorders Identification Test (AUDIT), may be helpful in achieving this. They are quick to administer, so applicable in primary care, and have been found to be superior to laboratory tests, including the best performing gamma-glutamyl transpeptidase (GGT) test (sensitivity 33%) at detecting excessive drinkers (>16 drinks (224 g) daily), with a sensitivity of 93%.[49] Clinicians should be vigilant for cognitive symptoms in such individuals. Neuroimaging in suspected alcohol-related cognitive impairment is an informative adjunctive source of information in the assessment. Cerebral atrophy (particularly of frontal white matter), white matter lesions and hippocampal atrophy are consistent with alcohol-related brain damage, although not discriminative from vascular or Alzheimer's dementias.

Recent associations between moderate alcohol intake and adverse brain outcomes should be highlighted in discussions with patients about their drinking. Any health benefits are likely to be limited to one unit (8 g) daily, and even this has increased risks of breast cancer. Justification of moderate drinking on the grounds of brain health has become a little harder.[50]

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REFERENCES

1. **Office for National Statatistics.** *Opinions and lifestyles survey: adult drinking habits in great britain*, 2014.
2. **Blazer DG,** Wu LT. The epidemiology of alcohol use disorders and subthreshold dependence in a middle-aged and elderly community sample. *Am J Geriatr Psychiatry* 2011;**19**:685–94.
3. **Office for National Statatistics.** *Omnibus survey report drinking: adults' behaviour and knowledge in 2009*.
4. **Cao Y,** Willett WC, Rimm EB, *et al*. *Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies*, 2015.
5. **Peterson JB,** Rothfleisch J, Zelazo PD, *et al*. Acute alcohol intoxication and cognitive functioning. *J Stud Alcohol* 1990;**51**:114–22.
6. **Kopelman MD,** Thomson AD, Guerrini I, *et al*. The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol Alcohol* 2009;**44**:148–54.
7. **Giancola PR,** Moss HB. Executive cognitive functioning in alcohol use disorders. *Recent Dev Alcohol* 1998;**14**:227-51.
8. **Sabia S,** Elbaz A, Britton A, *et al*. Alcohol consumption and cognitive decline in early old age. *Neurology* 2014;**82**:332–9.
9. **Kuźna E,** Llewellyn DJ, Langa KM, *et al*. History of alcohol use disorders and risk of severe cognitive impairment: a 19-year prospective cohort study. *Am J Geriatr Psychiatry* 2014;**22**:1047–54.
10. **Ritchie K,** Villebrun D. Epidemiology of alcohol-related dementia. *Handb Clin Neurol* 2008;**89**:845–50.
11. **Oslin D,** Atkinson RM, Smith DM, *et al*. Alcohol related dementia: proposed clinical criteria. *Int J Geriatr Psychiatry* 1998;**13**:203–12.
12. **Kril JJ,** Halliday GM. Brain shrinkage in alcoholics: a decade on and what have we learned? *Prog Neurobiol* 1999;**58**:381–7.
13. **Chanraud S,** Martelli C, Delain F, *et al*. Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology* 2007;**32**:429–38.
14. **Pfefferbaum A,** Sullivan EV, Mathalon DH, *et al*. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcohol Clin Exp Res* 1995;**19**:1177–91.
15. **Bengochea O,** Gonzalo LM. Effects of alcoholization on the rat hippocampus. *Neurosci Lett* 1991;**123**:112–4.
16. **Alvarez I,** Gonzalo LM, Llor J. Effects of chronic alcoholism on the amygdaloid complex. A study in human and rats. *Histol Histopathol* 1989;**4**:183–92.
17. **Zahr NM,** Pitel AL, Chanraud S, *et al*. Contributions of studies on alcohol use disorders to understanding cerebellar function. *Neuropsychol Rev* 2010;**20**:280–9.
18. **Ferrer I,** Fabregues I, Pineda M, *et al*. A Golgi study of cerebellar atrophy in human chronic alcoholism. *Neuropathol Appl Neurobiol* 1984;**10**:245–53.
19. **Harding AJ,** Halliday GM, Ng JL, *et al*. Loss of vasopressin-immunoreactive neurons in alcoholics is dose-related and time-dependent. *Neuroscience* 1996;**72**:699–708.
20. **Harper CG,** Kril JJ, Holloway RL. Brain shrinkage in chronic alcoholics: a pathological study. *BMJ* 1985;**290**:501–4.
21. **Sullivan EV,** Marsh L, Mathalon DH, *et al*. Relationship between alcohol withdrawal seizures and temporal lobe white matter volume deficits. *Alcohol Clin Exp Res* 1996;**20**:348–54.
22. **He J,** Crews FT. Increased MCP-1 and microglia in various regions of the human alcoholic brain. *Exp Neurol* 2008;**210**:349–58.
23. **Rimm EB,** Williams P, Fosher K, *et al*. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;**319**:1523–8.
24. **Stampfer MJ,** Colditz GA, Willett WC, *et al*. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med* 1988;**319**:267–73.
25. **Brust JC.** Ethanol and cognition: indirect effects, neurotoxicity and neuroprotection: a review. *Int J Environ Res Public Health* 2010;**7**:1540–57.
26. **Ruitenberg A,** van Swieten JC, Witteman JC, *et al*. Alcohol consumption and risk of dementia: the Rotterdam Study. *Lancet* 2002;**359**:281–6.
27. **Orgogozo JM,** Dartigues JF, Lafont S, *et al*. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. *Rev Neurol* 1997;**153**:185–92.
28. **Mukamal KJ,** Kuller LH, Fitzpatrick AL, *et al*. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA* 2003;**289**:1405–13.
29. **Ormstad H,** Rosness TA, Bergem AL, *et al*. Alcohol consumption in the elderly and risk of dementia related death--a Norwegian prospective study with a 17-year follow-up. *Int J Neurosci* 2016;**126**:135–44.
30. **Heffernan M,** Mather KA, Xu J, *et al*. Alcohol consumption and incident dementia: evidence from the sydney memory and ageing study. *J Alzheimers Dis* 2016;**52**:529–38.
31. **Anstey KJ,** Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry* 2009;**17**:542–55.
32. **Peters R,** Peters J, Warner J, *et al*. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing* 2008;**37**:505–12.
33. **Xu W,** Wang H, Wan Y, *et al*. Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2017;**32**:31–42.
34. **Stampfer MJ,** Kang JH, Chen J, *et al*. Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med* 2005;**352**:245–53.
35. **Ganguli M,** Vander Bilt J, Saxton JA, *et al*. Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology* 2005;**65**:1210–7.
36. **Lobo E,** Dufouil C, Marcos G, *et al*. Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? *Am J Epidemiol* 2010;**172**:708–16.
37. **Bos I,** Vos SJ, Frölich L, *et al*. The frequency and influence of dementia risk factors in prodromal Alzheimer's disease. *Neurobiol Aging* 2017;**56**:33–40.
38. **Luchsinger JA,** Tang MX, Siddiqui M, *et al*. Alcohol intake and risk of dementia. *J Am Geriatr Soc* 2004;**52**:540–6.
39. **Gu Y,** Scarmeas N, Short EE, *et al*. Alcohol intake and brain structure in a multiethnic elderly cohort. *Clin Nutr* 2014;**33**:662–7.
40. **Ding J,** Eigenbrodt ML, Mosley TH, *et al*. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2004;**35**:16–21.
41. **Mukamal KJ,** Longstreth WT, Mittleman MA, *et al*. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke* 2001;**32**:1939–46.
42. **Kubota M,** Nakazaki S, Hirai S, *et al*. Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *J Neurol Neurosurg Psychiatry* 2001;**71**:104–6.
43. **de Bruin EA,** Hulshoff Pol HE, Schnack HG, *et al*. Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers. *Neuroimage* 2005;**26**:536–45.
44. **Anstey KJ,** Jorm AF, Réglade-Meslin C, *et al*. Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosom Med* 2006;**68**:778–85.
45. **Fukuda K,** Yuzuriha T, Kinukawa N, *et al*. Alcohol intake and quantitative MRI findings among community dwelling Japanese subjects. *J Neurol Sci* 2009;**278**:30–4.
46. **Topiwala A,** Allan CL, Valkanova V, *et al*. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ* 2017;**357**:j2353.
47. **Au Yeung SL,** Jiang C, Cheng KK, *et al*. Moderate alcohol use and cardiovascular disease from Mendelian randomization. *PLoS One* 2013;**8**:e68054.
48. **Almeida OP,** Hankey GJ, Yeap BB, *et al*. Alcohol consumption and cognitive impairment in older men: a mendelian randomization study. *Neurology* 2014;**82**:1038–44.
49. **Bernadt MW,** Mumford J, Taylor C, *et al*. Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet* 1982;**1**:325–8.
50. **Welch KA.** Alcohol consumption and brain health. *BMJ* 2017;**357**:j2645.
51. **Bengochea O,** Gonzalo L. *Effect of chronic alcoholism on the human hippocampus*, 1990.
52. **Harding A,** Halliday G, Caine D, *et al*. Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain* 2000;**123**:141–54.