

Alcohol and Cognition in the Elderly: A Review

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Consumption of large amounts of alcohol is known to have negative effects, but consumption in smaller amounts may be protective. The effect of alcohol may be greater in the elderly than in younger adults, particularly with regard to cognition. However, the drinking pattern that will provide optimal protection against dementia and cognitive decline in the elderly has not been systematically investigated. The present paper is a critical review of research on the effect of alcohol on cognitive function and dementia in the elderly. Studies published from 1971 to 2011 related to alcohol and cognition in the elderly were reviewed using a PubMed search. Alcohol may have both a neurotoxic and neuroprotective effect. Longitudinal and brain imaging studies in the elderly show that excessive alcohol consumption may increase the risk of cognitive dysfunction and dementia, but low to moderate alcohol intake may protect against cognitive decline and dementia and provide cardiovascular benefits. Evidence suggesting that low to moderate alcohol consumption in the elderly protects against cognitive decline and dementia exists; however, because of varying methodology and a lack of standardized definitions, these findings should be interpreted with caution. It is important to conduct more, well-designed studies to identify the alcohol drinking pattern that will optimally protect the elderly against cognitive decline and dementia.

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INTRODUCTION

Consumption of large amounts of alcohol is known to have negative effects, but drinking smaller amounts may have a protective effect in adults of all ages. Since alcohol is distributed in body water, a given dose of alcohol will have a greater pharmacokinetic effects in the elderly because of their diminished body water compared to younger adults.¹ Elderly show markedly consistent pharmacodynamic profile reflecting early peak impairment and rapid acute tolerance,² in conjunction with less pharmacodynamic sensitivity.³ These suggest that alcohol consumption may have a greater affect on the elderly than on younger adults, particularly in relation

to cognitive function.¹ However, the systemized reviewed literatures concerning the optimum pattern of alcohol consumption to protect against dementia and cognitive decline in the elderly have been relatively lacking.

The influence of alcohol on health varies depending on the amount consumed, drinking duration, type of alcohol and frequency, environmental factors, and the genetic disposition of the individual. Low to moderate drinking (LMD) may be helpful for stress relief, relaxation, mood elevation, intimacy formation, and cognitive function.⁴⁻⁷ Furthermore, LMD may decrease the risk of cardiovascular disease (CVD), respiratory disease, stroke, and mortality.⁸⁻¹⁰ However, frequent heavy drinking or binge drinking may cause CVD, cancer and early death and is associated with alcohol abuse, intoxication, alcohol withdrawal, alcohol withdrawal delirium, alcohol dependence, alcohol-related cognitive impairment, and alcohol-related dementia (ARD), which may lead to severe social, economic, physical, and psychological burdens.¹¹⁻¹⁴ Moreover, excessive alcohol consumption may induce organic changes in the region of the frontal cortex primarily involved in cognition and inhibitory control; thus, the relationship between

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alcohol, cognition, and changes in frontal cortex structure have recently become the focus of clinical and neurobiological interest.^{12,15-17}

During the normal ageing process, deficits in frontal cortex function (including working memory, speed of information processing, decision-making, planning, and judgment) or retrieval of stored memory may appear, and the decline of semantic memory and verbal or crystallized intelligence is not clear.¹⁸ In addition to the effects of the normal aging process, the risk or prevalence of mild cognitive impairment and dementia appears to increase with age in the elderly.^{12,19,20} At present, no cure for dementia or therapeutic strategy to prevent the transition of mild cognitive impairment to dementia exist, but epidemiological evidence supports the hypothesis that a healthy lifestyle may prevent the development dementia in the elderly.^{18,21,22} Healthy life habits associated with a reduction in the risk of dementia are exercise, physical activity, healthy diet, and LMD.²³⁻²⁵ The type of alcohol and optimal level of consumption associated with a healthy lifestyle are not well understood, and studies of LMD and health often have methodological limitations, such as confounding effects of gender, racial/cultural differences, and comorbidities such as depression and substance use disorders. Thus, the outcomes of studies related to LMD are controversial and systematic reviews of evidence-based research are necessary.

The present review of evidence-based research may help determine the optimal alcohol drinking pattern to prevent cognitive decline and dementia in the elderly and provide an alternative to existing therapeutic interventions, which have limited effectiveness. Accordingly, the present paper is a review of the literature focusing on the influence of alcohol on cognition and dementia in the elderly. We searched the NCBI PubMed database (available at <http://www.ncbi.nlm.nih.gov>) within the last 10 years (2001 to 2011) using the key words: alcohol, ethanol, cognition, neuroprotection, neurotoxicity, elderly, mild cognitive impairment, and dementia. In some cases, earlier studies from the reference lists of relevant papers (1971 to 2000) were reviewed.

The authors first reviewed the neurotoxic effects of alcohol in the elderly with a focus on cognitive function and changes to brain structure related to psychiatric symptoms and disorders. We then reviewed the neuroprotective effect of alcohol on cognitive function and related changes to brain structure in the elderly with a focus on the optimal pattern and level of alcohol consumption to prevent cognitive dysfunction.

NEUROTOXIC EFFECT OF ALCOHOL

Mechanism of alcohol neurotoxicity

The brain is highly vulnerable to the neurotoxic effects of alcohol, and cognitive disorders may result from brain damage

caused by chronic alcohol abuse.²⁶ The neurotoxic effects of alcohol that cause cognitive deficits may be mediated directly through damage to brain structures or indirectly through malnutrition, metabolite toxicity, electrolyte imbalance, or accompanying physical illnesses including liver disease and infection.²⁷ The direct neurotoxic effect of alcohol is mediated via its action on the NMDA receptors of glutamatergic neurons. Acute alcohol intake exerts an inhibitory effect on NMDA receptors and, thus, induces receptor up-regulation, but when alcohol intake ceases, the up-regulated receptors are no longer inhibited, resulting in an excessive stimulation of NMDA receptors. This, in turn, causes an excessive influx of calcium with cytotoxic effects.²⁶ Glutamatergic neurons are densely concentrated in the frontal lobes and subcortical areas such as the hippocampus, and these brain regions are particularly vulnerable to excitotoxic effects produced by alcohol intake.²⁶ Thiamine deficiency and Korsakoff syndrome resulting from chronic alcohol abuse is an example of indirect alcohol neurotoxicity. Thiamine deficiency causes an excessive release of glutamate which, like alcohol, can exert a neurotoxic effect; in fact, chronic alcohol abuse and thiamine deficiency may have an additive or even synergistic neurotoxic effect.²⁸ Studies of amnesia in patients with Korsakoff syndrome have shown that the condition may have an anterograde component with inability to learn new information, and a retrograde component in which the recent memory is more impaired than remote memory, and a confabulation component associated with these memory defects.²⁹ The apolipoprotein E (APOE) epsilon 4 allele provides a possible genetic explanation for susceptibility to alcohol-induced neurotoxicity. Research findings suggest that people with the allele have a less effective neural repair mechanism and, thus, are more susceptible to the deleterious effects of alcohol.^{30,31} Elevated serum levels of homocysteine is related to alcoholism,³² and leads to increase of glutamatergic neurotransmission via overstimulation of NMDA receptors.³³ This plays a crucial role in the neurobiology of alcoholism, particularly regarding cognitive impairment,³⁴ brain atrophy,³⁵ and alcohol withdrawal seizures.³⁶ Regarding to alcohol neurotoxicity related to immune system, it is reported that chronic alcohol induces systemic cytokines particularly tumor necrosis factor alpha (TNF α). TNF α appears to involve potentiation of glutamate excitotoxicity and activates resident microglia inducing neuroinflammation.³⁷ There are the recent findings in microglia and astrocyte function toward neurotoxicity via reactive oxygen species under heavy alcohol consumption.³⁷⁻⁴⁰ Taken together, alcohol disruption of cytokines and inflammation contribute in multiple ways to a diversity of alcoholic neurotoxicity.

Other mechanisms that may influence alcohol-related neurotoxicity and cognitive dysfunction are free radical toxicity, acetaldehyde toxicity, modulation of the nicotinic acetylcholine

receptor, serotonin receptor, dopamine receptor, opioid receptor, and gamma-aminobutyric acid (GABA) receptor, but additional studies are necessary to confirm these findings.⁴¹⁻⁴⁴

Acute effect of heavy drinking on cognition

The common symptoms of acute alcohol neurotoxicity include cognitive impairment, blackout, and hangover. Heavy or binge drinking commonly causes acute alcohol intoxication, and blackouts may occur without loss of consciousness in this state.⁴⁵ After the intoxication has worn off, headache, dysphoric mood, tremor, fatigue, vomiting, loss of appetite, and diarrhea and gastrointestinal symptoms may persist for a considerable amount of time in the hangover.⁴⁶ Blackouts and hangovers occur prior to alcohol-related cognitive dysfunction and are clinically significant as predictive factors for brain damage that may cause transient cognitive impairment or more permanent cognitive dysfunction.^{47,48}

Alcohol intoxication during or after heavy alcohol consumption causes clinically maladaptive behavioral changes and physiological changes that may lead to impaired judgment, memory and attention damage, stupor, or coma.⁴⁹ Impairment in free recall, executive function, and visuospatial function are clearly observed at all ages in the state, and most of these symptoms are reversible after alcohol withdrawal.^{50,51}

A blackout may be complete (en-bloc) or partial (fragmentary) depending on the severity of memory impairment,⁵² and is related to impaired episodic memory, a type of memory encoded using spatial and social contexts.⁵³ Blackout is most consistently associated with a rapid increase in blood alcohol concentration. However, not all people who drink rapidly and excessively experience blackouts, suggesting that genetic disposition plays a role in determining brain vulnerability to alcohol. Alcohol-related blackouts may disturb the memory stages of encoding, storage, and retrieval (recall, recognition), and cause complete or partial deficits in retrieval. Blackouts may result from damage to the hippocampus which is involved in encoding memory at the cellular level, and antagonization of the N-methyl D-aspartate (NMDA) receptors which are necessary for the induction of long-term potentiation in the hippocampus at the molecular level.⁵⁴

Hangovers from alcohol intoxication are generally the result of binge drinking. Studies investigating the relationship between hangover and cognitive deficits have reported conflicting or negative results. This disparity may be the result of methodological differences involving the definition of hangover, alcohol dose, state (e.g., quality of sleep, mood, and uncontrolled behavior), type of tasks, and time of assessment after alcohol intake. However, recent studies using complex tasks to assess cognitive function when the level of alcohol were 0 found a decline in memory, attention, psychomotor performance, and frontal ex-

ecutive function during hangover. Further studies are necessary to verify these effects of hangover on cognition.⁵⁵

Cognitive decline in low to moderate drinking

Ryback⁵⁶ proposed a continuum of alcohol effects on cognition from light functional deterioration in LMD to serious cognitive deficits in heavy drinkers. Consistent with this hypothesis, early studies found cognitive deficits in abstraction and concept formation in young-to middle-aged men who engaged in social drinking,^{57,58} and two studies in women reported similar results.^{59,60} Two previous studies reported that LMD increased cognitive decline in the elderly,^{61,62} and one longitudinal study reported that LMD increased the risk of Alzheimer's disease.⁶³ A population-based study suggested that elderly low to moderate drinkers who were APOE epsilon 4 allele carriers were more likely to develop dementia compared with non-drinking and non-carrier counterparts.³⁰

Effect of low to moderate alcohol intake on brain structures

Increased brain shrinkage with a linear increase in ventricle size and sulci width has been reported in middle-aged⁶⁴ and elderly⁶⁵ chronic low to moderate drinkers according to the amount of alcohol consumed. Furthermore, a linear increase in white matter volume and decrease in grey matter volume in the frontal and parietal brain regions has been reported in middle-aged men who were chronic low to moderate drinkers.⁶⁶

Alcohol-Related Dementia in heavy drinking

The relationship between dementia and alcohol use is complex. Chronic heavy drinking may cause brain damage and give rise to ARD, a form of dementia that is clinically different from Alzheimer's disease and vascular dementia.⁶⁷ The concept of ARD is now recognized as Alcohol-Induced Persisting Dementia in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, and its diagnostic criteria must fulfill conditions such as alcohol-related multiple cognitive deficits that may cause significant impairment in social or occupational functioning, compared with the previous level of functioning. Furthermore, the symptoms cannot occur just during the course of delirium and must persist beyond the usual duration of substance intoxication or withdrawal.⁴⁹ This diagnosis, however, has been made entirely at the discretion of the clinician, and considerable controversy exists as to its clinical validity as a diagnostic entity.⁶⁸

Oslin et al.¹⁴ suggested that the ARD diagnostic criteria be subdivided into probable ARD, possible ARD, and mixed dementia modeled after the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association (NINCDS/ADRDA) diagnostic criteria for Alzheimer's disease. In a subsequent study,

Oslin et al.⁶⁷ independently verified the validity of these diagnostic criteria and reported that 24% of dementia patients had ARD and 10% of elderly nursing home residents were diagnosed with ARD. These diagnostic criteria continue to be widely used; however, consensus regarding their usefulness has not been reached, and further research is warranted.

The diagnostic algorithm developed by the authors (JWK and DYL) to facilitate the clinical diagnosis of ARD¹⁴ contains seven 'yes' or 'no' questions and is described as follows: 1) Is it dementia? (Dementia is defined as a significant deterioration of cognitive function sufficient to interfere with social or occupational functioning. As defined by DSM-IV,⁴⁹ this requires deterioration in memory and in at least one other area of intellectual functioning. Moreover, the cognitive changes cannot be attributable to the presence of delirium or substance-induced intoxication or withdrawal.) 2) Was the clinical diagnosis of dementia made at least 60 days after the last exposure to alcohol? 3) Was there significant alcohol use as defined by a minimum average of 35 standard drinks (SD) per week for men or 28 for women over a period greater than 5 years? [If 'yes', go to question 5, if 'no' go to question 4] 4) Was there significant alcohol use as defined by an average of 21-34 SD per week for men and 14-27 for women over a period greater than 5 years? 5) Did the period of significant alcohol use occur within 3 years of the initial onset of dementia? [If 'yes', go to question 7, if 'no', go to question 6] 6) Did the period of significant alcohol use occur 3-10 years prior to the initial onset of dementia? 7) Is there more than one cause for the dementia? The diagnostic interpretation of the algorithm is as follows. If the answer to questions 1, 2, 3, 5 is 'yes', the diagnosis is probable ARD. If the answer is 'yes' to questions 1, 2, 3, 6 or to 1, 2, 4, 5, the diagnosis is possible ARD. Finally, if the answer to questions 1 and 7 are 'yes', mixed dementia is diagnosed. A diagnosis of ARD is supported by the presence of any of the following: 1) alcohol-related hepatic, pancreatic, gastrointestinal, cardiovascular, or renal disease, or other end-organ damage; 2) ataxia or peripheral sensory polyneuropathy (not contributable to other specific causes); 3) the cognitive impairment stabilizes or improves after 60 days of abstinence; 4) neuroimaging evidence of ventricular or sulcal dilatation improves after 60 days of abstinence; 5) neuroimaging evidence of cerebellar atrophy, particularly in the vermis.^{14,67}

Several recent cohort and epidemiological studies using varying diagnostic criteria in people over 65 years of age have reported a high incidence of comorbid excessive alcohol intake and dementia or the increased risk of dementia and severe cognitive impairment.^{67,69-72} In people diagnosed with ARD, the cognitive deficit manifests as poor working memory, decreased verbal fluency, perseveration, circumstantiality, impaired abstraction, and decreased behavioral initiation,⁷³ and magnetic resonance imaging (MRI) scans show ventricular enlargement and diffuse at-

rophy disproportionately affecting the prefrontal regions.^{74,75} These neuropsychological deficits and brain damage may be partially reversed with continued abstinence.⁷⁶⁻⁷⁸

Marchiafava-Bignami disease in heavy drinking

Marchiafava-Bignami disease (MBD) is a rare toxic disease commonly found in chronic alcoholics. The exact cause is not known, but progressive demyelination of the corpus callosum is the pathological hallmark of this condition and anatomical pathology examination reveals demyelination and necrosis of the corpus callosum.⁷⁹ Clinically, this disease may start with stupor or coma. Upon recovery, seizure, dementia with complex attention deficits, memory and language difficulty, personality change, and signs of interhemispheric disconnection (e.g., left-hand anomia, apraxia, agraphia) may appear.^{80,81}

NEUROPROTECTIVE EFFECT OF ALCOHOL

Mechanism of alcohol neuroprotection

Several studies showing a lower risk of CVD in LMD compared with non-drinkers or heavy drinkers suggest a neuroprotective effect of alcohol.^{82,83} This cardioprotection has been attributed, in part, to an alcohol-induced elevation of high density lipoprotein cholesterol (HDL-cholesterol),⁸⁴ reduction of fibrinogen and other thrombotic factors,⁸⁵⁻⁸⁷ and reduction in the inflammatory marker C-reactive.⁸⁸ Furthermore, work in animals has shown that the neuroprotective effect is linked to interactions between alcohol and protein kinase C, the adenosine receptor, and cardioprotective proteins (e.g., superoxide dismutase, nitric oxide synthase, and heat shock protein). Moreover, the findings indicated that neuroprotection is correlated with the down-regulation of inducible nitric synthase and up-regulation of endothelial nitric oxide synthase.⁸⁶ Furthermore, a study in animals showed that ingestion of low to moderate levels of alcohol prior ischemic stroke protected against ischemia-induced brain damage by delaying neuronal death, neuronal and dendritic degeneration, oxidative DNA damage, glial cell activation, and neutrophil infiltration.⁸⁹ In addition to the antioxidant properties of alcohol itself, the antioxidant effect of polyphenols (such as resveratrol), which are abundant in red wine, has been proposed to be neuroprotective.⁹⁰⁻⁹² Moreover, low to moderate alcohol intake has been shown to act on cholinergic fibers in rats to stimulate prefrontocortical acetylcholine release.⁹³

The evidence strongly suggests that LMD acts via these neuroprotective mechanisms and benefits the brain and cardiovascular system by protecting against myocardial infarction, ischemic stroke, cognitive decline, vascular dementia, and Alzheimer's disease.⁹⁴

Effect of low to moderate alcohol consumption on cognition

Studies of the influence of LMD on cognition have reported varying results. Several earlier studies suggested that LMD did not decrease the risk of cognitive decline, including dementia,⁹⁵⁻⁹⁸ however, most of those studies had methodological limitations, such as cross-sectional design, small sample size, uncontrolled confounding factors, and variability in age, gender, and type of alcohol. Furthermore, LMD may be a proxy marker that reflects psychiatric and physical health and socio-economical position, and may be related to cognitive functions other than the mechanism that improves the vascular system described above;⁹⁹ thus, caution is required in the evaluation of the relationship between alcohol consumption and cognition.

An increasing number of reports suggest a U- or J-shaped relationship between cognitive function and amount of alcohol consumption, suggesting that LMD is more beneficial to cognition than non-drinking or heavy drinking.^{65,100-102} In contrast, several studies have reported limited or condition-specific benefits of alcohol on cognitive function. Launer et al.¹⁰³ found that alcohol improved cognitive function only in patients with CVD or diabetes mellitus, while other studies have reported a benefit in elderly women, but not men.^{104,105} Studies of the neuroprotective effect of the APOE epsilon 4 allele have reported neuroprotection in the presence of the allele,^{100,106} in the absence of the allele,^{94,107} and no effect in either its presence or absence.^{6,108}

In recent cross-sectional population-based studies of African Americans,⁷⁰ French men and women,¹⁰⁵ Japanese American,¹⁰⁹ LMD was found to have a greater cognitive benefit than non-drinking. Moreover, six large-scale longitudinal population-based studies reported similar results.^{6,108,110-113} According to a recent meta-analysis of 23 longitudinal studies (20 epidemiology cohort studies and three retrospective matched case-controls nested in a cohort) of alcohol consumption and cognitive decline or dementia in elderly people over 65 years of age, LMD significantly reduced the risk of dementia [risk ratio (RR) 0.63; 95% CI 0.53-0.75] and Alzheimer's disease (RR 0.57; 0.44-0.74) and showed a non-significant trend in reducing vascular dementia (RR 0.82; 0.50-1.35) and cognitive decline (RR 0.89; 0.67-1.17).¹¹⁴

Effect of low to moderate alcohol intake on brain structures

MRI results have revealed that chronic LMD may cause brain shrinkage,^{64,65} an increase in white matter volume, and a reduction in grey matter volume;⁶⁶ however, a recent study has reported partially conflicting results showing less white matter damage in elderly low to moderate drinkers compared with non-drinkers.²⁶ Furthermore, a U- or J-shaped relationship between alcohol consumption and an increase in brain volume was found

in elderly women who were light drinkers (<7 SD per week) relative to abstainers.¹¹⁵ Two studies reported no change in white and grey matter volume as a function of amount of alcohol consumed in middle-aged women relative to middle-aged men.^{66,116} These gender differences can be explained by the protective effect of estrogen against glutamate toxicity.⁶⁶ Elderly men who were low to moderate drinkers showed a reduction in white matter hyperintensity and an increase in grey matter volume in a U- or J-shaped pattern when compared with abstainers, and elderly women showed no change in either white or grey matter.¹¹⁵ Studies of white matter grade, which evaluate the degree of cortical white matter integrity, have reported no significant neuroprotective effect of LMD on white matter grade in men and women (middle-aged adults and older adults of 60-64 years old) under 65 years of age.^{64,115} However, a U- or J-shaped pattern between white matter grade and alcohol consumption has been reported in elderly LMDs over 65 years of age.^{65,117} Although studies of the relationship between LMD and changes in brain structure show varying results, overall, the evidence suggests that alcohol has a neuroprotective effect in the elderly.²⁶

Optimal alcohol consumption and type

The size and amount of alcohol contained in a SD differs from country to country, and no standard definition of LMD exists; thus, studies examining the cognitive benefits of LMD often have varying results. It is, therefore, critical that LMD and SD be standardized for future studies.

A recent systematic review using a meta-analysis to investigate optimal alcohol consumption to prevent cognitive decline in the elderly found no agreement on the optimal drinking pattern because the classification of LMD varied widely.¹¹⁴ Reports of the optimal consumption against cognitive decline in the elderly ranged from more than, less than, or equal to one drink a month¹¹³ or one drink a day,¹¹⁸ and one to two drinks per week in subjects with CVD or diabetes.¹⁰³ The optimal amount reported against Alzheimer's disease was weekly consumption of wine,¹¹⁹ one to six or more than two drinks per week,^{94,120} or more than three drinks/250-500 mL per day (usually wine),¹²¹ or when studied by gender, one to three drinks per day in men.^{100,120,121} Against dementia, benefit was shown with more than one drink per day, weekly, or monthly wine consumption, 250-500 mL (usually wine) or more than three drinks per day^{118,120-122} and from 1-28 units per week.¹²³ One to three drinks per day appeared to be beneficial for men against vascular dementia.¹⁰⁰

With regard to the alcohol type, the review of longitudinal studies on the influence of alcohol on cognitive function showed that there are mainly reports of cognitive benefit in wine,^{121,122} and there are reports of cognitive benefit regardless of alcohol type.^{6,94,108}

CONCLUSIONS

Heavy or binge drinking has neurotoxic effects regardless of age. Alcohol consumption may have a greater affect on the elderly via its pharmacological effects and ageing process than on younger adults, particularly in relation to cognitive function.

Longitudinal and brain imaging studies in the elderly show that excessive alcohol consumption may increase the risk of cognitive dysfunction and dementia, but LMD may protect against cognitive decline and dementia and provide cardiovascular benefits. Evidence suggesting that LMD in the elderly protects against cognitive decline and dementia exists. The present review of evidence-based research may help determine the optimal alcohol drinking pattern to prevent cognitive decline and dementia in the elderly and provide an alternative to existing therapeutic interventions, which have limited effectiveness. However, the varying results of several evidence-based studies of the benefits and risks of alcohol on cognition should be interpreted with caution. Furthermore, the cognitive benefit of LMD may vary from person to person; thus, it is difficult to make a clinical recommendation for abstainers to drink alcohol. Nevertheless, it is important to conduct well-designed studies to determine the optimal alcohol drinking pattern for the elderly as the alternative against cognitive decline and dementia.

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