Wine consumption, cognitive function and dementias – A relationship?

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Abstract. Healthy cognitive function is essential for quality of life, wellbeing and independent living, and is negatively associated with dementias. A series of longitudinal and neuro-imaging studies in the elderly have shown that light to moderate wine consumption is neuro-protective although heavy or abusive alcohol consumption is neuro-toxic. A J-shaped relationship between alcohol consumption, cognitive dysfunction and risk of dementias is also observed for younger and middle aged consumers. There is also no data to suggest that long-term light to moderate alcohol consumption exacerbates age-related cognitive decline and impairment. An optimal amount of wine for neuro-protection appears to be up to 30 g alcohol daily. There are multiple plausible biological mechanisms in various animal models, *in vitro* and *in vivo* for wine-derived phenolic compounds which go beyond their antioxidant activity and attenuation of oxidative stress.

Keywords: Alcohol, wine, cognitive function, dementia, Alzheimer's disease

1. Introduction

Cognitive function is defined as the intellectual or mental processes by which knowledge is acquired, including perception, reasoning, acts of creativity, problem-solving and possible intuition. Cognitive dysfunction or impairment is associated with increased disability and an increased need for institutionalised care. Dementia is a form of cognitive dysfunction whereby an individual loses the ability to think, remember and reason due to physical changes in the brain. There are at different types of dementias with different but inter-related causes and symptoms [1], the most prevalent of which is Alzheimer's disease followed by vascular dementia, dementia with Lewy bodies and frontotemporal dementia. This cognitive dysfunction eventually leads to a loss of independence that becomes a burden on families and society, as the individual requires more intense care and often institutionalisation [2]. In the later stages, the cognitive impairment associated with dementias will create total dependency such that dementias are the single greatest cause of disability in Australians aged 65 years or older, and the third leading cause of disability burden overall. Dementias are also the third leading cause of death in Australia (the second leading cause in women). As there is no cure, identification of factors associated with preservation of cognitive function could lead to substantial improvements in the quality of life in older Australians.

Damage to DNA, lipids and proteins by oxidative free radicals has been implicated in accelerated ageing, degenerative diseases including cancer [3], cognitive decline and impairment, Alzheimer's disease and other dementias [4, 5] and Parkinson's disease [6], as well as cardiovascular disease. Population ageing is occurring on a global scale, with faster ageing projected for the coming decades than has occurred in the past [7]. Globally, the population aged 60 years and over is projected to nearly triple by 2050, while the population aged 80 years and over is projected to experience a more than five-fold increase [8]. Diseases of old age are thus expected to increase significantly over the next few decades as people increasingly survive beyond the age of 80 years [9]. Consequently there is interest in identifying lifestyle factors and molecular mechanisms that

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can minimise the risk of these debilitating conditions, including simple dietary measures.

A systematic review of health behaviours which maintain healthy cognitive function suggests that the consumption of fish and vegetables [10, 11], moderate physical activity and moderate alcohol consumption tend to be protective against cognitive decline and dementia [12, 13]. Alcohol acts directly and indirectly on the central nervous system [14, 16, 115] and alcohol abuse causes cognitive impairment.

1.1. Systematic reviews and meta-analyses

There have been few systematic reviews on the effects of light to moderate alcohol consumption on cognitive dysfunction and dementias in elderly adults [17]. Cognitive health can be considered as a continuum of cognitive function ranging from optimal to decline to impairment and dementia [12, 18]. It was cautiously concluded from a meta-analysis of 23 studies that there was some evidence to suggest that alcohol consumption in earlier adult life may be protective against incident dementia later [19]. An examination of epidemiological studies published between 1998 and 2008 also suggested that light to moderate alcohol consumption may be associated with a 38% reduced risk of unspecified dementias and with a 32% reduced risk specifically for Alzheimer's disease. From a meta-analysis of 15 studies, Anstey et al. (2009) also concluded that light to moderate alcohol consumers later in life have a 47% reduced risk of any dementias compared with abstainers [20]. In addition, Neafsey and Collins (2011) concluded that in 14 of 19 countries for which data was available, light to moderate alcohol consumption significantly reduced the risk of cognitive decline and in the remaining countries there were non-significant reductions in risk as well [21]. Heavy drinking was, however, associated with an increased risk of cognitive decline and dementias. Their meta-analysis of 143 studies also differentiated between the different types of alcoholic beverages and found that wine was more protective than beer or spirits although this finding was based on a relatively small number of studies. The SU.VI.MAX2 cohort study also found that heavy beer but not wine consumption was associated with impaired cognitive function [22]. Long-term light to moderate alcohol consumption of any alcoholic beverage does not appear to exacerbate age-related cognitive impairment [23].

1.2. J-shaped relationship of alcoholic beverages with cognitive dysfunction

From prospective population-based studies, there is a clear J-shaped relationship between the consumption of alcoholic beverages such as wine, and the risk of cardiovascular diseases including myocardial infarction, which has been extended to a reduced risk of certain cancers, type 2 diabetes and ischaemic stroke [24–34]. Over the last decade, evidence has accumulated which suggests that this J-shaped relationship could also be extended to the risk of cognitive dysfunction and dementias such as Alzheimer's disease and vascular dementia [35–41]. Mild cognitive dysfunction or impairment is an early symptom of Alzheimer's disease.

While the literature consistently defines light to moderate consumption as 20 to 40 g ethanol per day [42, 43], several studies have defined moderate consumption as up to 80 g ethanol per day for men [41, 44], which may reflect country and cultural differences in alcohol consumption; 10 g ethanol approximates one drink or 100 mL wine. For amounts above moderate consumption the risk of alcohol-related diseases increases dose-dependently [45]. Interestingly, cognition has been observed to decline in individuals who ceased consuming alcoholic beverages [46, 47] and similarly declined with heavier consumption compared to light to moderate consumption [48, 152].

1.3. Relationship of alcoholic beverages to cognitive function and dementias in an ageing population

Prior to a study by Zuccala et al. (2001), there was conflicting evidence on the relationship between alcohol consumption per se and cognitive function [35, 41, 49–55].

Zuccala et al. (2001) analysed the association between alcohol consumption and cognitive impairment in 15,807 hospitalized older patients who were enrolled in an Italian multicentre pharmacoepidemiology survey [41]. The amount of alcohol use was recorded as daily wine units (100 mL or approximately 10 g ethanol), because wine, particularly with meals, represents the major form of alcohol consumption in this Italian population. The probability of cognitive impairment was reduced among male patients who reported an average daily alcohol consumption of 1 L or less of wine, as compared

with abstainers, but the probability increased among heavier drinkers. Among women, only the lightest-drinking category (less than 500 mL per day) showed a decreased probability of cognitive dysfunction when compared with abstainers, whereas heavier drinking was associated with an increased probability of cognitive impairment. The prevalence of alcohol abuse was similar among participants with cognitive impairment and those with normal cognitive functioning. The results of this study indicated that less than four drinks per day for women and less than eight drinks for men was associated with reduced probability of cognitive impairment as compared with abstinence, after adjusting for potential confounders. This nonlinear association persisted when cerebrovascular diseases and Alzheimer's disease were considered separately. Such a nonlinear association might explain the conflicting results of previous studies regarding the relationship between alcohol consumption and cognitive functioning. Elias et al. (1999) similarly observed a gender difference in amount of alcohol consumption necessary for improved cognitive function where 'superior' cognitive performance was found within the range of four to eight drinks per day for men but only two to four drinks per day for women, compared to abstainers [51].

A potential confounder which could explain earlier conflicting results is genetic differences in ability to metabolise alcohol. Although not consistently observed in studies [56], individuals with higher genetic ability to metabolise alcohol and who are hence less exposed to alcohol have been shown to have a greater association with healthy cognitive function than those with lower genetic ability [57]. The enzyme alcohol dehydrogenase (ADH) catalyses the metabolism of alcohol to acetaldehyde [58, 59]. There are, for example, at least nine different forms of ADH enzymes which are encoded by seven different genes. Each form of the enzyme has a different rate of metabolism and may be located in different tissues. Accordingly, the effect of alcohol consumption on cognition changes may be conditional on genotype.

Subsequent studies have also independently assessed the association between alcohol consumption and cognitive function and have affirmed the observations of Zuccala et al. (2001) but have also provided more detailed data [30, 41, 60–65]. For example, both current moderate alcohol consumption and cumulative lifetime alcohol consumption are associated with better cognitive function compared to abstainers. This improvement specifically encom-

passes baseline attention, processing speed, which is the ability to perform tasks requiring rapid visual scanning and mental processing of information, memory such as verbal knowledge or memory including immediate and delayed recall, recognition memory, figural memory and working memory, as well as motor speed. This has been observed for both men and women [62, 66–69]. Gross et al. (2011) concluded that that the consumption of alcoholic beverages three to four times per week or low levels of drinks per week through midlife and into later life, confers the best cognitive outcomes in old age, as defined by word-finding ability in late life, a measure of executive function [70]. These relationships were independent of age, smoking status, hypertension, gender, and correlations with other cognitive test scores.

As mentioned earlier, mild cognitive dysfunction is an early symptom of dementia, and in particular Alzheimer's disease, which is a complex, late-onset disorder characterised by the loss of memory and multiple cognitive functions. In patients with mild cognitive dysfunction, consuming up to 15 g alcohol per day now appears to also decrease the rate of progression to dementia by approximately 85% [71], while 10–30 g alcohol per day reduces the risk of Alzheimer's disease and vascular dementia [72–74].

1.4. Alcohol consumption in younger and middle aged adults and effects on cognitive function and dementias

In addition to observations of a J-shaped relationship for older adults with alcohol, studies have also noted a J-shaped relationship between cognitive dysfunction and alcohol consumption in young and middle-aged adults [21]. For example, from an Australian study of 7485 adults aged 20–64 years, male consumers drinking up to 20 g alcohol per day and female consumers drinking up to 10 g alcohol per day were observed to have better cognitive function than abstainers, occasional and heavier consumers [75]. Recent research has also shown that that mid-life diet and lifestyle behaviours contribute to cognitive health in older adults, suggesting cumulative effects of diets and lifestyles. Clustering of multiple risk factors increases the risk of dementia [76]. Conversely a reduction or removal of these risk factors reduces the risk, or delays the onset, of cognitive decline and dementias [12], indicating the advantages of adopting a healthy diet and lifestyle that includes moderate alcohol consumption.

1.5. Relationship of wine to cognitive function and dementias

Moderate wine consumption rather than alcohol consumption per se has been specifically associated with a lower risk of developing dementia and specifically Alzheimer's disease in studies over the past two decades [38, 54, 72–74, 77–84]. Wine consumption of up to approximately 75 mL per day improved cognition in 883 elderly subjects recruited from the Norwegian Hordaland Health Study [154]. From the Personnes Agées Quid (PAQUID) study of 3,777 subjects aged 65 years and older who were followed for three years, in the 922 subjects drinking between 125 to 250 mL per day the odds ratio was 0.55 for Alzheimer's disease [153]. In the 318 subjects drinking between 250 and 500 mL per day, however, the odds ratio was 0.19 for incident dementia and 0.28 for Alzheimer's disease compared to the 971 non-drinkers after adjusting for age, sex, education, occupation and other possible confounders. In the Washington Heights Inwood-Columbia Aging Project, 980 community-dwelling individuals aged 65 and older without dementia at baseline were recruited between 1991 and 1996 and followed annually [38]. After four years of follow-up, 260 individuals developed dementia and, of these, 199 developed Alzheimer's disease. After adjusting for age, gender, apolipoprotein E (APOE)-epsilon 4 status, education, and other alcoholic beverages, only consumption of up to 33 g alcohol per day as wine was associated with a lower risk of Alzheimer's disease.

Consistent with observations of effects of moderate wine consumption on cognitive decline, both current and cumulative lifetime moderate wine consumption were associated with a reduced risk of dementias compared to abstainers [85]. For example, after controlling for potential confounders, current wine consumption of between 20 to 29 g per day was associated with a 29% decrease in the incidence of overall dementias and a 49% decrease specifically in the incidence of Alzheimer's disease. These wine consumers also had better physical as well as mental health.

A primary difference between wine and the other alcoholic beverages is that wine contains phenolic compounds similar to those contained in fruits, vegetables and teas, the consumption of which has also been associated a lower incidence of both mild cognitive dysfunction, dementias such as Alzheimer's disease and other cerebrovascular/neurodegenerative diseases [86–90].

1.6. Potential biological mechanisms of action for ethanol and wine-derived phenolic compounds

More than 500 compounds have been identified in *Vitis vinifera* grapes and wine to date [91, 92]. Wine typically contains alcohols such as methyl, ethyl, n-propyl, iso-propyl, iso-butyl, iso-amyl, act-amyl, 2-phenethanol, n-hexanol as well as detectable amounts of approximately 18 other alcohols, where the most abundant alcohol is ethyl alcohol or ethanol [93]. The concentration of ethanol in 'table' wine generally ranges between 8 and 15% v/v [94]. Wine also typically contains phenolic compounds and their polymeric forms and the total amount of phenolic compounds in a 100 mL glass of red wine is approximately 200 mg versus 40 mg in a glass of white wine [94]. Chemically, phenolic compounds are cyclic benzene compounds possessing one or more hydroxyl groups associated directly with an aromatic ring structure. Wine-derived phenolic compounds include the non-flavonoid classes of compounds such as hydroxycinnamates, hydroxybenzoates and stilbenes such as resveratrol, as well as the more abundant flavonoid classes of compounds including flavan-3-ols, flavonols and anthocyanins. Of these, resveratrol appears to have been the most widely examined phenolic compound over the past decade. While polymeric condensed tannins and pigmented tannins constitute the majority of red wine phenolic compounds, their large size precludes absorption and they are thus unlikely to contribute to any biological mechanisms [95]. Data from animal studies suggest that grape- and wine-derived phenolic compounds are absorbed and accumulate in the brain in measureable amounts after multiple or repeated oral doses [96, 97]. Wine-derived phenolic compounds, and particularly resveratrol, have been shown be cerebro- or neuroprotective in various models, *in vitro* and *in vivo*, and potential mechanisms have been proposed. Data from similar studies using different varieties of red wines with different profiles of phenolic compounds, as well as studies comparing different phenolic compounds, suggest that the individual classes of phenolic compounds may exhibit differential effects in the brain [98, 99]. From Scholey et al. (2014), the consumption of 100 mL of red wine with a relatively low concentration of resveratrol resulted in better performance by elderly subjects during Series Threes of Cognitive Demand Battery tests, compared with consumption of that same wine enriched with 100 mg resveratrol, while the resveratrol-enriched red wine resulted

in better performance during Serial Sevens [155]. Serum analysis confirmed absorption of resveratrol and its metabolites.

Different biological mechanisms of action have been proposed for the observed benefits of light to moderate wine consumption on cognitive function in later life.

1.7. Haemostasis and oxidative stress

The beneficial effects of alcoholic beverages such as wine on the risk of cardiovascular and cerebrovascular diseases have been partly attributed to changes in lipid and haemostatic or blood flow factors. These changes include ethanol-induced increases in the concentration of high density lipoprotein-cholesterol, and ethanol- and phenolic-induced increases in the thrombolyic 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. 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. (2006) 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 [63]. This suggests then that ethanol and phenolic compounds such as resveratrol may impact cognition through a separate vascular or degenerative pathway [100]. 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 [101]. Indeed, among older persons without cerebrovascular and neurodegenerative diseases, those who moderately consume alcoholic beverages such as wine have been shown to have fewer white-matter abnormalities and infarcts on magnetic resonance imaging than abstainers [102], where pronounced reductions in the risk of both vascular dementia and Alzheimer's disease have been shown among persons consuming one to six standard drinks per week [23].

A lack of heme oxygenase 1, an endogenous enzyme that is induced in neurons in response to oxidative and other stress and stimulates the degradation of pro-oxidant heme into free iron, carbon monoxide and biliverdin and/or the anti-oxidative bilirubin, may also be associated with increased neural damage from ischaemic strokes [103], as well with Alzheimer's disease and Parkinson's disease [104]. Heme oxygenase 1 is dose- and time-dependently induced by resveratrol, which may provide another cerebrovascular and neuroprotective effect for phenolic compounds.

Indeed, Parkinson's disease has been linked to increased levels of oxidative and nitrosative stress [105, 106], and is characterised by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta region of the brain and the appearance of Lewy bodies and neurites, which comprise insoluble amyloid-like fibrils that contain the protein alpha-synuclein. Oxidative stress apparently promotes the aggregation of alpha-synuclein [107]. An inverse relationship between amount of wine consumed and risk has been observed where the lowest risk was observed for wine consumers of approximately 140 to 420 g per week [108]. Wine-derived phenolic compounds such as catechin and epicatechin have recently been observed *in vitro* to inhibit the formation of alpha-synuclein fibrils, and to destabilize preformed fibrils [109].

1.8. Neurotransmission

Cognitive function is also associated with acetylcholine. Cognitive decline associated with dementias, Huntington's disease and Parkinson's disease, as well as with Down's syndrome and multiple sclerosis, is characterised neurochemically by a consistent deficit in cholinergic neurotransmission, in particular in the cholingeric neurons in the basal forebrain. Inhibition of acetylcholinesterase which restores cholinergic neurotransmission, also appears to prevent the aggregation of amyloid-β peptides and formation of amyloid fibrillar plaques [110].

Ethanol 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 [111]. In contrast, quercetin inhibits acetylcholinesterase [112]. Indeed, acetylcholinesterase inhibitors which reversibly bind and inactivate the enzyme that degrades acetylcholine are the primary medications prescribed associated with mild improvements in cognitive function. The impairment of memory performance by chronic and heavy consumption, however, parallels the reduction of acetylcholine neurotransmission.

Concerning Alzheimer's disease, which is associated with the presence of intracellular neurofibrillary tau tangles, extracellular amyloid-β (Aβ) peptides, synaptic failure, mitochondrial dysfunction and depletion of acetylcholine, it has been suggested that ethanol may directly stimulate the release of acetylcholine in the hippocampus [111]; synaptic levels of acetylcholine decrease as a result of cholinergic neuron involvement. In a rat model, a moderate concentration of ethanol (0.8 g/kg) stimulated the release of acetylcholine while a higher concentration (2.4 g/kg) inhibited its release [115]. The formation of amyloid fibrillar plaques is also common in diseases such as Parkinson's disease, prion diseases, Down's syndrome and type II diabetes [116–121].

Another important intracellular signalling system involved in learning and memory is protein kinase C (PKC), a family of 12 serine/threonine kinases [122]. PKC modulates cell viability which protects certain neuronal cells against Aβ-induced toxicity. Resveratrol and other phenolic compounds such as epigallocatechin gallate have been observed to protect hippocampal cells against Aβ-induced toxicity by activating PKC [113, 123, 124], and specific binding sites for resveratrol have been identified in the rat brain [114], as have receptors for the green tea catechin gallates.

1.9. Amyloid-β factors and Alzheimer's disease

Amyloid-β (Aβ) is a core component of the plaque or lesion found in the neocortex and hippocampus of brains affected by Alzheimer's disease [117, 125, 126]. It is formed after sequential proteolytic cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein. APP can be processed by α-, β- and γ-secretases. Unlike α-secretase which cleaves APP into non-toxic amyloid-α, the toxic amyloid-β protein is generated by successive action of the β and γ secretases. The γ secretase, which produces the C-terminal end of the amyloid-β peptide,

cleaves within the transmembrane region of APP and can generate a number of isoforms of 39–43 amino acid residues in length. The most common isoforms are Aβ_{40} and Aβ_{42}; the shorter form is typically produced by cleavage that occurs in the endoplasmic reticulum, while the longer form is produced by cleavage in the trans-Golgi network. The Aβ_{40} form is the more common of the two, but Aβ_{42} is the more fibrillogenic or polymeric and is thus associated with disease states, promoting pro-inflammatory responses and activating neurotoxic pathways leading to neuronal dysfunction, and the death and loss of neurons [127]. Inhibition of the accumulation of amyloid β-peptides and the formation of Aβ fibrils/plaques from amyloid β–peptides, as well as the destabilization of preformed Aβ fibrils/plaques in the brain would, therefore, be attractive therapeutic targets for the treatment of Alzheimer's disease and other related neurodegenerative diseases.

As mutations in APP associated with early-onset Alzheimer's disease have been noted to increase the relative production of Aβ_{42}, a potential therapy may involve modulating the activity of β and γ secretases to produce mainly A$\beta_{40.}$ Administration of a red wine equivalent to two standard drinks to Tg2576 mice, which model Alzheimer's disease Aβ neuropathology and corresponding cognitive deterioration, has been shown to promote the non-amyloidogenic processing of the APP, which acts to prevent the generation of the amyloid-β peptide [128]. For example, administration of red wine reduced amyloidogenic Aβ_{1-40} and Aβ_{1-42} peptides in the neocortex and hippocampus of Tg2576 mice and correspondingly decreased the neocortical Alzheimer's disease associated amyloid fibrils/plaque. Subsequent examination of APP processing and amyloid-β peptide generation increased the concentration of membrane-bound α-carboxyl terminal fragments of APP in the neocortex and α-secretase activity was also increased, while there was no significant change in the neocortical concentration of β and γ carboxyl terminal fragments of APP or in β and γ secretases activity.

The typical red wine-derived phenolic compounds catechin, quercetin, epicatechin, myricetin and tannic acid have, however, been shown *in vitro* to dose-dependently inhibit the formation of Aβ fibrils from fresh Aβ_{1-40} and Aβ_{1-42}, as well as their extension, and also to dose-dependently destabilise preformed Aβ fibrils [129–131]. Only resveratrol, however, has been shown to decrease the level of intracellular Aβ produced by different cell lines expressing the wild type of Swedish mutant amyloid-β precursor protein

(APP$_{695}$) by promoting its intracellular degradation [132]. This mechanism was proteasome-dependent, that is, resveratrol appears to activate the proteasome involved in the degradation of Aβ, as the resveratrol-induced decrease of Aβ could be prevented by several selective proteasome inhibitors and by siRNA-directed silencing of the proteasome subunit β5. Resveratrol does not inhibit the production of Aβ because it has no effect on β and γ secretase activity.

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. Grape-seed phenolic compound extract, which primarily comprises catechin and epicatechin in monomeric, oligomeric and polymeric forms, has been shown *in vitro* and in animal studies to inhibit Aβ aggregation into high molecular weight oligomers [133]. This inhibition coincided with attenuation of Alzheimer's disease-type cognitive impairment. Resveratrol and its glucoside, piceid, have, however, been shown *in vitro* to dose-dependently inhibit the formation of Aβ fibrils [134, 135]; other stilbene monomers examined are less potent inhibitors. Binding may be induced by hydrophobic interactions between the phenolic rings and the hydrophobic region of Aβ, thus blocking associations between Aβ molecules and inhibiting fibril formation. These interactions may then be reinforced by the H-bond between the hydroxyl group of the phenolic rings and some donor/acceptor groups of Aβ, as observed for other peptides.

1.10. Amyloid-β and APOE-epsilon 4 allele

In the Washington Heights Inwood-Columbia Aging Project (1991−1996), however, a lower risk was confined to wine consumers without the APOE-epsilon 4 allele [38], which has also been observed in several similar studies [74, 136, 137]. This allele is implicated in atherosclerosis, Alzheimer's disease and impaired cognitive function, possibly influencing the increased deposition of amyloid-β in the brain as it is less effective compared to other alleles at facilitating the proteolytic break-down of this peptide, both within and between cells [138].

Indeed, the most important genetic risk factor for Alzheimer's disease is the apolipoprotein E (ApoE)

genotype. ApoE is a protein that carries lipids in and out of cells. It occurs in three isoforms: ApoE2, ApoE3, and ApoE4. The gene for ApoE is on chromosome 19. One copy is inherited from each parent. The most common ApoE allele is ApoE3. Individuals who are homozygous for the ApoE4 allele develop Alzheimer's disease earlier at a mean age of 70 years. Furthermore, individuals homozygous for the ApoE4 allele, as well as tobacco smokers and heavy alcohol consumers are more likely to be diagnosed with Alzheimer's disease approximately 10 years earlier than those with none of these three risk factors [139]. The ApoE4 allele is also a risk factor for hypercholesterolemia. ApoE4 has been detected in neurofibrillary tangles and in Aß [38]. This suggests that ApoE lipoproteins participate in some way in the processing of APP, perhaps by modulating APP secretases, and may also play a role in the assembly of the neuronal cytoskeleton. High cholesterol levels during mid-life increase the risk of Alzheimer's disease and lipid-lowering therapies including the consumption of wine-derived phenolic compounds can lower this risk which may accordingly lower the risk of developing Alzheimer's disease [140–142].

1.11. Regional brain volumes

As brain structure and volume are associated with cognitive function [143, 144], it may be assumed that they could be similarly associated with alcohol consumption. For example, intracranial area and several regional brain volumes appear correlated with tests of premorbid and fluid intelligence and tests of visuospatial memory. Several studies that have examined these associations have shown conflicting results [145–148]. The collective findings of these studies, however, suggest that light to moderate alcohol consumption, particularly wine, is associated with both improved cognition and larger total brain volume, which may be reduced in individuals consuming heavier amounts of alcohol. Replication of these studies is required.

2. Conclusions

In the elderly in particular, but also in younger adults, light to moderate wine consumption is associated with neuro-protective effects although binge and heavy alcohol consumption is neuro-toxic [17, 149]. There is also a relationship between the neuro- and

cardio-protective effects of wine, given that reducing the risk of atherosclerosis and coronary heart disease also lowers the risk of cognitive impairment [150, 151]. Consistent with cardioprotection, an optimal amount of wine for neuro-protection appears to be up to 30 g alcohol daily [152].

There are plausible biological mechanisms in various animal models, *in vitro* and *in vivo* for the wine-derived phenolic compounds in reducing the risk of cognitive dysfunction and dementias. These mechanisms support a cerebro- or neuro-protective role for catechin, quercetin and resveratrol, in particular, which go beyond their antioxidant activity and attenuation of oxidative stress. More research is required on their intracellular and molecular targets and hence protection, and it would be unwise to extrapolate these results to humans without longer-term clinical studies in patients experiencing extensive neuronal loss associated with dementias and other neurodegenerative diseases. Considering the multiple plausible biological mechanisms, these compounds provide promise as therapeutic or prophylactic agents in neurodegenerative diseases.

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