

# Alcohol and Dementia – What is the Link? A Systematic Review

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Caspar Wiegmann<sup>1</sup>  
Inge Mick<sup>1</sup>  
Eva J Brandl<sup>1</sup>  
Andreas Heinz<sup>1,2</sup>  
Stefan Gutwinski<sup>1</sup> 

<sup>1</sup>Department of Psychiatry and Psychotherapy, Psychiatric Hospital of Charité at St. Hedwig Hospital, Berlin, Germany; <sup>2</sup>Department of Psychiatry and Psychotherapy, Charité University Medicine Berlin, Berlin, Germany

**Background:** Dementia is a globally increasing health issue and since no cure is currently available, prevention is crucial. The consumption of alcohol is a controversially discussed risk factor for dementia. While many previously published epidemiological studies reported a risk reduction by light to moderate alcohol consumption, there is no persuasive model of an underlying biochemical mechanism. The purpose of this article is to review current models on alcohol neurotoxicity and dementia and to analyze and compare studies focusing on the epidemiological link between alcohol consumption and the risk of dementia.

**Methods:** The electronic database Pubmed was searched for studies published between 1994 and 2019 concerning the topic.

**Results:** Available epidemiological studies are not sufficient to verify a protective effect of alcohol on dementia development.

**Keywords:** alcohol neurotoxicity, Alzheimer's disease, vascular dementia, Korsakoff's syndrome

## Introduction

Psychotropic drugs are used in nearly every culture and alcohol is the most widely and growingly used recreational drug.<sup>1</sup> Worldwide, only approximately 57% of the population have not consumed alcohol in the past 12 months.<sup>1</sup> There is a broad consensus that consumption of alcohol has potential adverse effects and is of relevance to the global burden of disease. Over 200 health conditions are linked to harmful alcohol use, ranging from liver diseases, road injuries and violence,<sup>2</sup> to cancers, cardiovascular diseases, suicides, tuberculosis, and HIV/AIDS.<sup>3</sup>

Dementia is considered a health priority by the WHO.<sup>4</sup> It has been estimated that 50 million people suffer from dementia and 10 million people are newly diagnosed with dementia every year.<sup>4</sup> A helpful distinction is made between primary and secondary dementia pathologies. Primary dementia forms include neurodegenerative dementia (Alzheimer's disease, frontotemporal dementia, Lewy-body-dementia) and vascular dementia. Secondary dementias are a consequence of other underlying systemic or brain diseases (such as vitamin deficiencies, infectious diseases, brain tumors).<sup>5</sup> To date, there is no effective cure for primary dementia forms, apart from arguable effects of acetylcholine esterase inhibitors (rivastigmine, donepezil, galantamine) and NMDA-receptor-antagonist (memantine) for Alzheimer's disease.<sup>6</sup> Therefore, the WHO considers the risk reduction a cornerstone of the action plan against dementia and seeks to strengthen the evidence base, share and disseminate evidence to support policy interventions for reducing potentially modifiable risk factors for dementia.<sup>4</sup>

Correspondence: Caspar Wiegmann  
Psychiatrische Universitätsklinik der Charité im St. Hedwig-Krankenhaus,  
Große Hamburger Str. 5-11, Berlin-Mitte  
10115, Germany  
Tel +49 30 2311 2500  
Email caspar.wiegmann@charite.de

In Alzheimer's disease, two main pathologies are detected microscopically: intracellular aggregates of hyperphosphorylated tau protein, a microtubule-associated protein in neurofibrillary tangles and dystrophic neuritis<sup>7</sup> and extracellular plaques of mainly insoluble A-beta-40 fragments of the protein beta-Amyloid-precursor protein ( $\beta$ -APP).<sup>8</sup> The relation of cause and effect or interplay of these two pathologies with neurodegeneration and dementia is subject of ongoing debates. Vascular dementia is the result of microangiopathy and macroangiopathy. Since the etiology of the two most common forms of dementia is very different, the consumption of alcohol might interact via different biochemical pathways in dementia development and lead to variable effects dependent on the dementia type.

The effects of light to moderate alcohol consumption on cognitive performance and the risk of developing dementia are controversially discussed,<sup>9–11</sup> especially concerning the effect of low-dose alcohol on vascular pathology and the existence of a specific alcohol-related dementia.<sup>12,13</sup> Different dosage definitions, ages at study inceptions, risk stratifications, lengths of assessment intervals and lengths of studies lead to different outcomes in a large number of epidemiological studies concerning low-dose alcohol consumption, while high doses of alcohol have most certainly a detrimental effect on cognitive performance<sup>14</sup> and can lead to a specific amnesic syndrome (Korsakoff's syndrome).

The purpose of this review is to give an overview about the dose- and pattern-related effects of alcohol on the risk of developing dementia, while trying to differentiate different neurodegenerative, vascular and other forms of dementia. The first part of the review will give an overview about alcohol effects on the central nervous system and summarize findings with different methodological approaches (biochemical methods, histopathological findings, animal models, neuroimaging). In the second part, we will present the results of a systematic literature search we conducted. We will then address the question whether alcohol consumption constitutes a potential target for dementia prevention.

## Methods

For the narrative review of alcohol effects and neurotoxicity, no systematic approach was applied. For the systematic review of epidemiological findings, the electronic database PubMed was searched to locate scholarly research examining the relationship between alcohol and dementia. The keywords dementia and alcohol were used as search entry. All studies with at least 250 participants, standardized dementia diagnosis protocol and published in English between the 1st of January 1994 and 1st of September 2019 were analyzed for information

concerning the link between alcohol consumption and dementia risk. Gender-specific or beverage-specific studies were excluded from analysis for pragmatic reasons: discussion of gender-specific effects or beverage-specific effects (for example, wine<sup>15</sup>) are beyond the scope of this review.

## Alcohol Effects on the Central Nervous System

### Acute Effects of Alcohol

Alcohol usually refers to the molecule ethanol. As amphiphile, it is rapidly absorbed from the stomach and duodenum after oral consumption and passes the blood-brain barrier. The distribution and elimination show strong variability due to fed- or fasting state, drinking patterns, age, and genetics.<sup>16</sup> In the central nervous system, ethanol modulates the function of multiple receptors: voltage-gated calcium channels and glutamate receptors are inhibited by alcohols, whereas some others, such as  $\gamma$ -amino butyric acid type A (GABA-A) receptors, glycine receptors, n-acetylcholine- and 5-HT<sub>3</sub>-receptors, are potentiated.<sup>17,18</sup> Prior hypotheses on the effect of alcohol on cell membrane function in the central nervous system are viewed as less relevant to its acute effects.<sup>17</sup> The effects appear to be dose-related, since at low dosages alcohol affects monoaminergic transmission and produces disinhibition and euphoria, while at high dosages anxiolytic and sedative effects are more prominent, mediated through increasing GABA activity and inhibiting excitatory amino acids.<sup>18</sup>

### Molecular Mechanisms of Central Nervous System Toxicity

In humans, chronic alcohol exposure leads to in vivo up- (glutamate) and down-regulation (D<sub>2</sub>,<sup>19</sup> GABAA) of neuroreceptors availability related to alcohol withdrawal and craving (for a summary see Heinz et al<sup>20</sup>). Genetic constitution interacts with monoaminergic dysfunction in alcohol withdrawal.<sup>21</sup>

Adaptive up-regulation of NMDA-receptors and consecutively enhanced calcium influx is supposed to contribute to cell apoptosis ("excitotoxicity") and link the acute and chronic effects of alcohol consumption.<sup>22,23</sup> The alcohol metabolite acetaldehyde was shown to be directly neurotoxic.<sup>24</sup> Other probable causes of cell death are inflammatory processes via release of pro-inflammatory cytokines and microglia activation after high dose alcohol consumption<sup>25</sup> Alcohol activates oxidases in the central nervous system, which leads to formation of free radicals and cell membrane damage.<sup>23</sup> Homocysteine is elevated after consumption of higher doses of alcohol and might contribute to alcohol-related brain damage.<sup>26</sup>

While these three mechanisms may underlie the more unspecific neurotoxic effects of alcohol, thiamine deficiency caused by malnutrition and decreased intestinal absorption in alcohol-dependent individuals shows distinct neuroanatomical patterns and symptomatology, which Karl Wernicke and Sergei Korsakoff already described accurately in the nineteenth century.<sup>27,28</sup> While Wernicke specified an acute neurological syndrome (stand and gait ataxia, confusion, and ophthalmoplegia), the overlapping Korsakoff's syndrome refers to more chronic alterations and symptoms, mainly perseveration and anterograde amnesia. Marchiafava-Bignami-Syndrome refers to thiamine deficiency-associated degeneration of the corpus callosum presenting with a wide array of symptoms including altered mental state, loss of consciousness and epileptic seizures (see Table 1 for details)<sup>29</sup>

Neurotoxicity of acetaldehyde, excitotoxicity and via NDMA-activation, neuroinflammation, and formation of free radicals as neuroanatomically less specific mechanism of neurotoxicity and thiamine deficiency with specific neuroanatomical susceptibility (corpora mammillaria, dorsal thalamic nucleus, hippocampus, periaqueductal region, corpus callosum) supposedly amplify each other, explaining the variety of neuropsychiatric symptoms in patients with high levels of alcohol consumption (for details on the correlation of etiology of neurotoxicity with neuroanatomy see Zahr et al<sup>30</sup>).

The entity of alcohol-related dementia is still controversially discussed, since there is no consensus whether it represents an entity distinct from Korsakoff syndrome and neuropsychological findings are unspecific,<sup>31</sup> encompassing cortical and subcortical patterns.<sup>12</sup>

## Neuropathology and Neuro-Imaging Studies

Autopsy studies show mild cerebral atrophy and lower mean brain weight in cases of uncomplicated alcoholism, when the

individual was not affected by Wernicke-Korsakoff encephalopathy.<sup>32</sup> The loss in brain volume is mainly attributed to white matter loss,<sup>30</sup> diffusion tensor magnetic resonance imaging (MRI) show fiber tract degeneration.<sup>33</sup> Histopathological studies revealed cerebellar atrophy,<sup>34</sup> corpus callosum thinning<sup>35</sup> and pyramidal cell loss in superior frontal and frontal association cortex,<sup>35</sup> as well as neuronal dendritic shrinkage, presumably reversible in abstinence.<sup>32</sup>

MRI studies have generally confirmed postmortem studies by demonstrating that these patients have regional cortical volume deficits,<sup>36-38</sup> conceptualized as accelerated aging.<sup>38</sup> MRI cohort studies show a correlation between cerebral volume decrease and number of drinks consumed.<sup>39,40</sup>

## Potentially Positive Effects of Alcohol on the Central Nervous System

A variety of positive effects on alcohol on the central nervous system have been suggested, mainly by reducing cardiovascular risk factors. Robust evidence exists for elevated high-density lipoprotein cholesterol blood levels,<sup>41</sup> even exceeding the effect of drugs prescribed for dyslipidemia.<sup>42</sup> The coagulation cascade is modulated by alcohol intake through down-regulation of fibrinogen, a substrate of blood clot formation.<sup>43</sup> In vitro experiments show an inhibition of platelet aggregation.<sup>44,45</sup> High alcohol consumption leads to higher blood pressure, while low to moderate consumption (equal or less than two drinks per day) has no effect.<sup>44,46</sup> The definition of one standard drink and consecutively, the definition of low-risk consumption varies in-between countries.<sup>47</sup> In the references cited, the US-American definition is used: one drink equals 14 g of pure alcohol. Nevertheless, any alleged positive aspects of drinking on cardiovascular risk factors must be weighed against seriously harmful effects, including changes in circulation, inflammatory response, oxidative

**Table 1** Thiamine Deficiency Associated Neurological Syndrome

Syndrome, Publication	Symptomatology	Pathology
Wernicke Encephalopathy - Carl Wernicke, Germany, 1881 <sup>28</sup>	Acute onset of ophthalmoplegia, ataxia, and mental confusion <sup>14</sup>	Hemorrhagic lesions in the mamillary bodies (confusion), hypothalamic nucleus, the periaqueductal region, pons, superior vermis of cerebellum <sup>88</sup>
Korsakoff's Syndrome - Sergej Korsakoff, Moscow, 1887 <sup>27</sup>	Severe memory loss, anterograde amnesia, confabulation, disorientation <sup>8</sup>	Lesions in the diencephalon-hippocampal circuit: midline thalamus, anterior thalamic nuclei <sup>88</sup>
Marchiafava-Bignami-Syndrome - Ettore Marchiafava, Amico Bignami, Rome 1913 <sup>89</sup>	Altered mental state, impaired walking, loss of consciousness, dysarthria, pyramidal signs, impaired memory, seizures <sup>29</sup>	Necrosis and atrophy in the corpus callosum <sup>29</sup>

stress, as well as anatomical damage to the cardiovascular system, especially the heart itself.<sup>48</sup>

## Effects of Alcohol on Alzheimer's Pathology

Regarding effects of alcohol on Alzheimer's disease (AD)-related pathophysiology, only scarce and contradictory evidence exists: in rats, alcohol application leads to higher acetylcholine release in the hippocampus in low concentrations, while higher concentrations inhibit acetylcholine release.<sup>49</sup> The hippocampus is affected early in Alzheimer's disease by formation of neurofibrillary tangles and neurodegeneration, leading to the typical early symptom of disability to memorize new information.<sup>7</sup>

Findings from transgenic mouse models and cell culture models of AD are contradictory. One study on transgenic AD-mice and hippocampal cell cultures established a possible mechanism of lower A $\beta$ -toxicity through alcohol administration by reducing A $\beta$ -induced synaptic failure,<sup>50</sup> another study argued that A $\beta$ -aggregation is reduced in cell cultures treated with alcohol.<sup>51</sup> However, findings from experiments conducted in a different transgenic mouse model fed with alcohol showed higher expression of APP and  $\beta$ -secretase with consecutively elevated amyloid deposition and neurotoxicity.<sup>52</sup>

Alcohol is supposed to enhance neuroinflammation and thereby enhancing neurotoxicity of the  $\beta$ -amyloid cascade.<sup>53</sup> In vitro studies suggest that alcohol might impede phagocytosis of  $\beta$ -amyloid by microglia and thereby promote Alzheimer's disease.<sup>54</sup>

In summary, while a number of studies have reported experimental findings to explain risk reduction through alcohol consumption for vascular dementia, data regarding the impact of alcohol on Alzheimer's pathophysiology is more contradictory.

## Epidemiological Findings Concerning Alcohol Consumption and Risk of Dementia

A number of studies have been published with different study designs (cross-sectional studies, cohort studies, case-control studies), inclusion criteria, alcohol dosage standardization and dosage definitions, type of alcoholic beverages included, endpoints (only Alzheimer's disease or all forms of dementia, mild cognitive impairment), and consumption patterns. Therefore, these studies show very heterogeneous outcomes.<sup>10,55–67</sup>

While a selection of studies is discussed below, [Table 2](#) gives an overview of all published studies in compliance with our inclusion criteria.

## Case-Control-Studies

A case-control-study of Bachmann and colleagues analyzed three assumed major risk factors (head trauma, smoking, and alcohol consumption) for dementia in African and European American individuals with dementia and their non-affected siblings.<sup>68</sup> Alcohol consumption over an average of 0.25 US standard drinks per day was associated with a lower dementia risk in both groups (relative risk 0.88/0.82, respectively). Risk factors did not vary in African and European Americans, while exposure was different in both groups (the proportion of European Americans drinking more than 0.25 drinks was higher than in African-Americans). A study by Mukamal and colleagues showed a higher effect (OR 0.46 for 1–6 standard US drinks, 0.69 for 7–13 standard US drinks) for low to moderate consumption in a subsample analysis of the Cardiovascular Health Study. Three hundred and seventy-three incident dementia cases were compared to 373 control cases, while thoroughly controlling for various covariates (educational level, marital status, income, diabetes, physical activity, ApoE-genotype).<sup>69</sup>

## Cohort Studies

In the Rotterdam Study, a large cohort study in elderly patients (over 55 years old), moderate drinking was defined as 1–3 drinks per day (no definition of grams of alcohol) and resulted in a significant risk reduction for any form of dementia, especially vascular dementia (RR 0.58/0.29, 38 patients in the group of moderate drinkers (1443) compared to 62 in the group of abstainers (1113)). The study achieved a high follow-up rate of 99.7% within an average follow-up period of 6 years. The analysis was adjusted for age, sex, systolic blood pressure, education, smoking, and body-mass index.<sup>10</sup>

The Whitehall-II-Study confirmed these findings in a younger population of civil service employees aged 35–55 years at study inclusion (9087 participants of which 397 developed dementia).<sup>70</sup> Similar to the Rotterdam Study, the risk for developing dementia was lowest in the individuals consuming between 1 and 14 drinks per week compared to abstainers (UK standard drink equals 8 g of alcohol). The hazard ratio for abstinence compared to consumption of 1–14 drinks per week for developing any kind of dementia was 1.47, after

adjusting for confounders (extensive assessment of socio-demographic data and cardiovascular health data). Diagnosis was made through linkage with mental health services data set, mortality register and national hospital episode statistics.

The 90+ study from California, USA could not establish alcohol as a risk factor for dementia for the very elderly living in a community for elderly people, after adjusting for age-, sex- and education. After an average follow-up period of 36 months, 268 of 587 had developed dementia of any kind. Neither the alcohol consumption at the first assessment (20 years earlier) nor on the second assessment at the age over 90 years correlated with the risk of dementia.<sup>58</sup>

Taking these three exemplary studies together, it may be argued that light-to-moderate alcohol consumption is protective against dementia in middle to late life, while the effect abates in the very elderly, but other cohort studies show different trends.

The HUNT study from Norway, encompassing almost the whole population of a community in Northern Norway (40,435 participants) showed no association of dementia with low or moderate alcohol consumption (only frequency of consumption measured).<sup>56</sup> An analysis from one of the largest twin cohorts worldwide (12,326 participants, Sweden) corroborates the risk of consuming high amounts of alcohol, while showing no effect of light to moderate consumption.<sup>71</sup> Relative to co-twins drinking light amounts, moderate-to-heavy drinking twins had a greater risk of dementia by 57% and reduced age of dementia onset by 4.76 years, while differences between lightly drinking or abstinent twins were non-significant.

An increasing number of cohort studies from different countries continue to be published. The results are heterogeneous concerning light to moderate consumption, while there is a consensus regarding high consumption and elevated dementia risk (see Table 2).

## Cross-Sectional Studies

Since Alzheimer's disease risk rises with ageing,<sup>10</sup> an alternative approach to study the effect of alcohol on Alzheimer's disease is to measure the age of onset in Alzheimer's disease patients exposed to putative risk factors. An earlier average onset in exposed individuals is an indicator of a higher relative risk. A study of Harwood and colleagues in a cohort of patients with Alzheimer's disease showed that patients who had been drinking more than two US standard drinks a day before the onset of dementia were on average diagnosed with dementia 4.1 years earlier

than patients that never drank,<sup>72</sup> a finding corroborated by the study of Handing and colleagues.<sup>71</sup>

## Epidemiological Studies of Electronic Health Data

A recent retrospective study of hospital discharge records encompassing about 80% of all discharge diagnoses in France (31624156 patient records) established an alcohol use disorder as major risk factor for developing any form of dementia, especially early-onset dementia.<sup>9</sup> The study set the diagnosis of alcohol use disorder in the patient discharge records in relation with a later diagnosis of a dementia. While this approach relies on hospital diagnoses with probable underestimation of both dementia and alcohol use disorders and although the amount of alcohol consumed could not be measured, the sample size and setting corroborates the high external validity of the results.<sup>73</sup> A Danish study using hospital admissions records and a German study using general health practitioners' treatment records replicated these results.<sup>10,74</sup>

## Meta-Analyses

A vast number of meta-analyses and reviews exist to the subject, mostly confirming the j-shaped correlation.<sup>75-79</sup> It has to be taken into account that meta-analysis adopts and merges the partially variable definitions of light to moderate consumption. Anstey and colleagues included 22 studies with 29,868 participants on alcohol consumption and dementia of any cause or cognitive decline.<sup>77</sup> Low to moderate consumption correlated to a lower OR for dementia (AD: 0.72 VaD: 0.75). A meta-analysis of Peters et al showed lower OR for any form of dementia in alcohol consumer than abstainers (OR for AD: 0.57, VaD: 0.82, 23 studies included).<sup>76</sup> There was no information given on controlled variables and the total number of participants.

In a dose-response analysis by Xhu and colleagues, 10 studies were used to calculate the weekly dose associated with the lowest risk of dementia of any cause: 6 g per day.<sup>59</sup> Varying assessment of consumption patterns (drinks per week, grams per day, etc.) complicated the analysis. A repeated evaluation using hazard ration rather than odds ratio is being planned.<sup>80</sup> The publication of Ilomäki and colleagues gives an overview about existing reviews and meta-analyses<sup>78</sup> and observes a positive effect of light alcohol consumption (<14 units per week) on any form of dementia.

**Table 2** Overview Over Epidemiological Studies on the Link Between Alcohol Consumption and Dementia with Cohorts of Over 250 Participants Since 1994 Until the 1st September 2019, Listed on PubMed. Studies Which Do Not Diagnose Dementia with Standardized Protocol Including Neuropsychological Assessment, MRI (Magnetic Resonance Imaging) and Examination by a Psychiatrist and/or Neurologist are Not Mentioned. No Gender-Specific Studies or Beverage-Specific Studies are Mentioned. Only Studies Published in English are Mentioned. Multiple Analyses of Same Cohorts Were Excluded. The Effect Summary in Bold Letters Refers to the Effect of Low to Medium Dose Alcohol Consumption as Defined in the Study, as Definitions Vary. AD (Alzheimer's Disease), HR (Hazard Ratio), MCI (Mild Cognitive Impairment), MMSE (Mini Mental State Examination), OR (Odds Ratio)

Cohort Studies				
Author, Year	Participants (Dementia Cases)	Cohort Description,	Follow-up	Finding
Yoshitake et al, 1995 <sup>55</sup>	828 (103)	Aged over 65, non-demented at inception, Kyushu, Japan	7 years, continuous assessment, 99.8% follow-up	<b>No effect:</b> alcohol consumption was not significantly associated with AD Limitations: vague measurement of alcohol intake (current consumption: yes/no)
Broe et al, 1998 <sup>60</sup>	327 (47)	Aged over 75, Sydney, Australia	3 years, 2 assessments	<b>No effect:</b> alcohol consumption was not significantly associated with AD Limitations: very aged cohort (mean age 83.4 years), low power to detect effects
Huang et al, 2002 <sup>61</sup>	402 (66)	Aged over 75, one district of Stockholm, Sweden	7 years, 3 assessments, 91% follow-up	<b>Protective effect:</b> Lower risk of AD in patients consuming between 1–14 drinks per week (women) or 1–21 drinks per week (men), OR 0.5. Limitations: Participants had already low MMSE scores at study inception (<25). Sample was predominantly female (81.8%). When patients with MMSE>24 were included, the result was not significant.
Ruitenberget al, 2002 <sup>10</sup>	7983 (197)	Aged 65 or older, residents of a Rotterdam suburb, Netherlands	7 years average, 4 assessments, 99.7% follow-up	<b>Protective effect:</b> Lower risk of all-cause dementia and vascular dementia in individuals consuming 1–3 drinks/day Limitations: standard drink was not defined in terms of grams
Lindsay et al, 2002 <sup>62</sup>	4088 (194)	Aged over 65, Nationwide Canadian cohort	5 years, 2 assessments	<b>Protective effect:</b> Regular alcohol consumption was associated with lower risk of AD (OR 0.68) Limitations: alcohol consumption was categorized as “regular consumption” or “no regular consumption”
Truelsen et al, 2002 <sup>63</sup>	1709 (83)	Aged over 65 at inception, residents of Copenhagen, Denmark,	Interval of 15 years in between alcohol assessment and dementia assessment	<b>No effect:</b> the risk of all-cause-dementia was elevated in the group of heavy drinkers (15–21 drinks per week, OR 2.26), effect disappears when controlled for co-variables (age, sex, years of education, history of stroke, income, cohabitation status, smoking, systolic blood pressure)
Luchsinger et. al, 2004 <sup>64</sup>	980 (260)	Aged over 65 at inception, residents of New York City, USA	4.1 years (mean), annual assessment	<b>No effect:</b> neither light to moderate (1–3 drinks/day) nor heavy alcohol consumption (>3 drinks/day) was associated with risk of AD or all-cause-dementia Limitations: alcohol intake was measured on one occasion

(Continued)

Table 2 (Continued).

Cohort Studies				
Author, Year	Participants (Dementia Cases)	Cohort Description,	Follow-up	Finding
Anttila et al, 2004 <sup>65</sup>	1018 (48)	Aged 42–56 at inception, inhabitants of two regions in Finland (Kuopio and Joensuu)	23 years (mean), 2 assessments	<b>Protective effect:</b> frequent drinkers (more than once a month) and abstainers (more than once a month) had higher OR for all-cause-dementia than infrequent drinkers (less than once a month) Limitations: very broad category of frequent drinkers ApoE4 enhanced the effect of frequent drinking (combined OR 7.07)
Ogunniyi et al, 2006 <sup>66</sup>	2480 (187)	Aged 65 or older; two cohorts from Indianapolis, USA (only African Americans) and Yoruba, Nigeria	5 years, 3 assessments	<b>Protective effect:</b> Alcohol consumption was associated with lower incidence of AD in both cohorts, but with lower OR (0.49) and significance only in the cohort from Indianapolis Limitations: low percentage of alcohol consuming participants, even lower in the Yoruba cohort
Deng et al 2006 <sup>67</sup>	2632 (121)	Aged 60 or older cohorts from six departments in China,	2 years, 2 assessments	<b>Protective effect:</b> Lower risk of AD in individuals consuming 1–21 units of alcohol (OR: 0.63) Limitations: only 84 AD cases
Langballe et al, 2015 <sup>56</sup>	40,435 (1084)	Aged 38–81 years at inception, cohort of an entire region of Northern Norway,	27 years, 2 assessments, 98.2%	<b>Risk factor:</b> no effect of low-dose alcohol consumption (less than five times during the last 14 days) on all-cause dementia, HR 1.4 for consumption of five or more times during the last 14 days for all-cause dementia. Limitations: no standardization of dementia diagnosis, no estimation of total alcohol dose
Heffernan et al 2016 <sup>57</sup>	821 (48)	Aged between 70–90 at inception, cohort of community dwelling participants from Sydney, Australia	4 years, 2 assessments	<b>No effect</b> on any form of dementia Limitations: short follow up of four years might underestimate long-term effects
Paganini-Hill et al, 2016 <sup>58</sup>	547 (268)	Participants of the 90+ study, aged over 90 at inception from California, USA	26 years, 3 assessments, 95% follow-up	<b>No effect</b> on any form of dementia Limitations: data partially obtained via telephone and relatives
Xue et al, 2017 <sup>59</sup>	437 (MCI), 106 (AD)	Aged over 65 at inception in 2010, participants with MCI, community-dwelling from Taiyuan, China	5 years, up to 10 assessments	Study on the risk of transition from MCI to AD <b>Risk factor:</b> light to moderate drinkers (<2 drinks per day) showed higher HR for transition from MCI to all-cause dementia Limitations: assessment of only MCI patients, small sample, broad definition of alcohol dose
Sabia et al, 2018 <sup>70</sup>	9087 (397)	aged 35–55 at inception; cohort from London civil service employees	23.2 years (mean), 5 assessments	<b>Protective effect:</b> risk for developing all-cause-dementia lowest in the individuals consuming between 1–14 drinks per week compared to abstainers and heavier drinkers

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Table 2 (Continued).

Cohort Studies				
Author, Year	Participants (Dementia Cases)	Cohort Description,	Follow-up	Finding
Schwarzinger et al 2018 <sup>9</sup>	31 624 156 (1 109 3434)	Cohort of all discharged patients in metropolitan France aged over 20 years at inception	5 years, continuous assessment	<b>Risk factor:</b> Risk of dementia elevated in patients diagnosed with alcohol use disorder, hazard ratio 3.3 for all type dementia Limitations: use of discharge diagnoses, no standardized assessment of neither alcohol use nor dementia diagnosis
Case Control Studies				
Author, Year	Participants (dementia cases)	Cohort description		Finding
Bachmann et al 2003 <sup>68</sup>	2779 (844)	Mean age 70 years, American patients with dementia and non-demented siblings		<b>Protective effect:</b> white participants consuming moderate (0.25–2 drinks/day) to high (>2 drinks per day) levels of alcohol showed a lower OR (0.88) of all-cause dementia compared to abstainers. Limitations: Number of African American participants was low (343)
Mukamal et al 2003 <sup>69</sup>	746 (373)	Aged over 65 years at inception, cohort subsample of the cardiovascular health study, USA		<b>Protective effect:</b> the subgroups drinking less than 1 drink (OR 0.65), 1–6 drinks (OR 0.46), 7–13 drinks (0.69) had a lower risk of all-cause dementia than abstainers Thorough assessment of covariates
Twin Studies				
Author, Year	Participants (dementia cases)	Cohort description	Follow-Up	Finding
Handing et al, 2015 <sup>71</sup>	12326 (1958)	Swedish twin cohort born between 1907 and 1925, aged between under 65 at inception	Up to 43 years	<b>No effect:</b> of low (1–5g/day) and moderate (6–12g/day) alcohol consumption in comparison to abstainers, elevated risk for heavy drinkers (>12g/day) Limitations: Diagnosis of dementia assessed only through death registry +Very long follow-up
Järvenpää et al, 2005 <sup>90</sup>	826 (103)	Finnish twin cohort, aged over 65 at assessment for dementia in 1999–2001	Up to 25 years	<b>No effect:</b> low-dose alcohol consumption was not associated with higher or lower risk Binge drinking or passing out had a very high OR for developing all-cause-dementia 25 years later (4.2/11.8) Limitations: Dementia was assessed by interview only, no neuropsychological assessment
Cross-sectional studies				
Author, Year	Participants (dementia cases)	Cohort description		Finding
Harwood et al 2009 <sup>72</sup>	685 (685)	Cohort of patients of a memory clinics in Miami, USA		<b>No effect:</b> only heavy drinking (>2 drinks per day) was associated with an earlier onset of AD compared to abstainers Limitations: age of onset was evaluated by interviews with caregivers

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Table 2 (Continued).

Cohort Studies				
Author, Year	Participants (Dementia Cases)	Cohort Description,	Follow-up	Finding
Toure et al, 2012 <sup>91</sup>	507 (47)	Cohort of patients of Social and medical center in Dakar, Senegal, aged over 65		<b>No effect:</b> alcohol had no effect on dementia risk Limitations: low percentage of alcohol consumption and dementia cases
Pilleron et al, 2015 <sup>92</sup>	1772 (135)	Two cohorts from the Central African Republic and Republic of Congo, aged over 65 at inception		<b>Protective effect:</b> participants consuming any amount of alcohol had a lower risk of all-cause-dementia (OR 0.34) Limitations: generally low levels of alcohol consumption and dementia in the whole cohort
Radford et al, 2018 <sup>93</sup>	381 (45)	Cohort of Aboriginal Australians, aged over 65 years at inception		<b>Protective effect:</b> low-risk alcohol consumption (audit-c) had lower OR for all-cause dementia than abstinence Limitations: Aboriginal Australians differ in terms of rates of illiteracy and education level from the general Australian population
Meta-Analyses				
Author, Year	Participants (dementia cases)	Cohort description		Finding
Anstey et al, 2009 <sup>94</sup>	14 studies included in the meta-analysis AD: 14646 Vascular D: 10225 ( All-cause-dementia: 11875	Different cohorts: Australia, Canada, China, France, Germany, Japan, Netherlands, Nigeria, Sweden, UK, USA		<b>Protective effect:</b> light to moderate drinkers OR 0.72 for AD and 0.74 for vascular dementia Limitations: dosage definitions vary in different studies included
Peters et al, 2008 <sup>76</sup>	23 studies included in the meta-analysis; Total number of included participants not given, in all studies showing significant results: 29,946 participant	Different cohorts: Australia, Canada, France, Finland, Germany, Japan, Netherlands, Sweden, UK, USA,		<b>Protective effect:</b> participants consuming small amounts of alcohol show lower risk of AD (RR 0.57) and all-cause dementia (0.63) but not for vascular dementia (0.82) Limitations: dosage definitions vary in different studies included
Tyas et al, 2010 <sup>95</sup>	3 only Canadian case-control-studies included	3cohorts from Canada		<b>No effect</b> Limitations: high inconsistency, use of secondary data
Wei-Xu et al, 2017 <sup>79</sup>	11 studies with 73,330 participants and 4586 cases of all-cause dementia	11 cohorts from China, Denmark, Finland, Netherlands, Norway, Sweden, USA		Dose-response analysis with the most beneficial dose being 6g alcohol/day or 2x/week <b>Protective effect:</b> consumption of less or equal of 2x/week, 7.5 drinks/week or 12.5g/day were associated with lower risk of all-cause-dementia Limitations: dosage definitions vary in different studies included

## Discussion

What can we deduce from the vast amount of studies and meta-analyses concerning alcohol consumption and dementia risk? Obviously, only correlations and not causal relationships can be deduced from cohort studies, since unmeasured factors

could be mainly responsible for both drinking behavior. Nonetheless, low to average alcohol consumption does not appear to increase the risk of dementia significantly or might be even protective. For both vascular dementia and Alzheimer's disease low- to moderately consuming

individuals show lower odds for dementia than abstainers and the effects are very similar when comparing the two dementia etiologies.<sup>10,69,70</sup>

This finding evidently leads us the question of possible confounders. The difficulty of assessing the consumed amounts is apparent; all reviews face rely on personal declaration of alcohol consumption and different definitions of one drink (from 8 g to 12 g of alcohol<sup>47,69,70</sup>) and the definition of heavy, moderate or light drinking vary.<sup>78</sup> It can be assumed that underreporting of alcohol consumption is a limitation to all studies related to alcohol consumption. In a Norwegian study, encompassing 88% of the population of a region, the average self-reported alcohol intake was lower than the statistically expected dose from other sources (statistics on sale, estimated self production and tourist import of alcohol).<sup>56,81</sup>

The group of abstainers, which is commonly used as reference group, includes former drinkers, who are abstinent only because they already suffer from consequences of their former drinking habits or take medication incompatible with alcohol consumption (“sick quitters hypothesis”).<sup>69</sup>

The majority of studies do not assess lifetime drinking trajectories. One study showed smaller effects (less cognitive decline in moderate drinkers) if former drinkers (“quitters”) were excluded from the group of abstainers.<sup>82</sup> Another study found a 20–60% higher risk of dementia in former drinkers.<sup>69</sup> This must be viewed as a cogent objection to supposed protective effect of light-moderate alcohol consumption.

In the patient cohorts included, alcohol use disorders might be severely underrepresented. Over 95% of patients with Alzheimer’s disease have a late onset and are over 65 years of age. People with alcohol use disorder are estimated to have a much lower life expectancy. A Scandinavian register study showed that people hospitalized with alcohol use disorder have an average life expectancy of 47–53 years (men) and 50–58 years (women) and die 24–28 years earlier than people in the general population, even though they have, presumably in contrast to other countries, wide access to the health-care system.<sup>83</sup> In a cohort study from Norway, the group that failed to report their alcohol consumption showed the highest risk of dementia, which might be explained by a high proportion of heavy drinking and consecutive high dementia risk.<sup>56</sup> In a study of centenarians, on the other hand, only 11% of the centenarian-males and 22% of the centenarian-females indicated to never consume alcohol.<sup>84</sup>

The retrospective cohort study of Schwarzingger et al showed the impressive increase in (mainly early onset) dementia risk in patients with alcohol use disorder.<sup>9</sup> This patient group would not have been included in most prospective cohort studies assessing alcohol use and dementia risk in the elderly, because of their already present dementia at the date of study inception.

Most prospective cohort studies have follow-up periods of two to three years (see Table 2). Due to the adverse effects on other organ systems<sup>22</sup> and higher mortality of alcohol-consuming individuals, these subjects may decrease in-between intervals (attrition bias). It has been shown that patients with Alzheimer’s disease-consuming alcohol decrease more rapidly than abstinent AD patients.<sup>59</sup> This attrition effect could lead to an underestimation of AD cases in the group of drinkers especially in prospective cohort studies with long intervals between data acquisition.

Alcohol consumption is a marker for several lifestyle factors. Moderate drinkers are leaner, more physically active, more often married and of higher socioeconomic status. A higher socioeconomic status (highest education degree and income) is associated with higher alcohol consumption in the elderly.<sup>85</sup> Higher education and higher socioeconomic status are known to be protective against dementia.<sup>86</sup> The lower risk of developing dementia in moderate drinkers might therefore be, at least partially be explained by their higher socioeconomic status. Only a randomized controlled trial could sufficiently establish causality – but would be difficult to conduct concerning the consumption of a widely consumed and potentially toxic substance.

Since we excluded gender- and beverage-specific studies, no conclusions can be drawn concerning different effects for men or women or effects of specific ingredients of alcoholic beverages other than alcohol. This review is also limited by the use of only one database. An even greater amount of evidence concerning the link between dementia and alcohol consumption might be gathered by using further databases and including publications in languages other than English for a more thorough systematic review.

## Conclusion

High-level alcohol consumption (>14 drink units/week) is certainly linked to an increase in dementia risk, post-mortem reduction in brain volume and MRI signs of brain damage via possibly multiple pathways.

Concerning low-level consumption of alcohol no recommendation to begin drinking moderate doses of alcohol in

higher age to reduce dementia risk can be deducted, because (1) results of studies are heterogeneous (2) the detrimental effects on other organ systems and risk of addiction; (3) the possible confounders in the studies presented and (4) because of the varying individual metabolism (gender, body weight, acetaldehyde dehydrogenase type<sup>16</sup>) and susceptibility. On the other hand, there is no rationale either, to recommend cutting down on alcohol consumption to reduce dementia risk if consumption is moderate (disregarding other risks of alcohol consumption).

A prospective, randomized, controlled trial could distinguish between direct, alcohol-related effects, statistical confounders, and lifestyle effects,<sup>87</sup> while more insight on the pathogenesis of Alzheimer's disease in general and more specifically the influence of alcohol on the different biochemical pathways could provide a cogent model of alcohol effects on dementia pathogenesis and progression.

## Disclosure

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