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ALCOHOL AS A RISK FACTOR FOR DEMENTIA: A REVIEW OF ETHANOL-INDUCED NEUROTOXICITY AND ITS MECHANISM

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ABSTRACT

Dementia is a significant public health concern that is expected to worsen in the future due to the growing proportion of elderly people in the population. One of the important and modifiable risk factors for this condition is alcohol consumption. The effect of alcohol on the development of dementia is dose-dependent; excessive intake increases the overall risk of developing dementia and also leads to a characteristic alcohol-induced neurocognitive disorder, sometimes referred to as alcohol-related dementia. Even moderate alcohol intake results in detectable changes in the brain, observable from a young age. These effects are caused by alcohol-induced neurotoxicity, including mechanisms such as neuroinflammation, the production of reactive oxygen species (ROS), acetaldehyde toxicity, and thiamine deficiency. This review summarizes the impact of alcohol consumption on the development of dementia, as well as the mechanisms of neurotoxicity caused by ethanol and its metabolic products.

Methodology: The study was based on scientific articles available in the PubMed and Google Scholar databases.

KEYWORDS

Alcohol, Dementia, Brain Atrophy, Alcohol Neurotoxicity

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Introduction

Dementia is a set of symptoms caused by brain damage. It is characterized by impairments in thinking, memory, behavior, and daily functioning. [1] The World Health Organization (WHO) has recognized dementia as a public health priority, which represents a serious and growing concern. In 2015, dementia affected approximately 47 million people worldwide, and according to the projections, this number is expected to rise to 75 million by 2030 and 132 million by 2050. [2]

Risk factors for dementia can be categorized into non-modifiable and modifiable. Non-modifiable factors include advanced age (primarily), sex, and genetic predisposition. Modifiable risk factors are the primary targets for preventive interventions. They can be divided into early-life, psychological, lifestyle, and cardiovascular risk factors [1]. Evidence suggests that addressing these risk factors may reduce the overall risk of developing dementia. Given the projected increase in the proportion of people aged 65 years and older- from 9% in 2019 to 16% in 2050 [3], an age group particularly at risk of developing dementia, preventive action is crucial.

One of the modifiable risk factors for dementia is ethanol exposure. Overall, studies indicate that excessive alcohol consumption (>21 UK units or >12 US units) increases the risk of developing dementia symptoms. [4]

Epidemiology of drinking

WHO has analyzed the global alcohol consumption patterns. In 2019, 56% of the population aged 15 and over abstained from alcohol. The remaining population consumed alcohol, on average 27 grams of pure alcohol per day. The average is elevated due to a small group of heavy drinkers who consume over 60 grams of pure alcohol per day, either episodically or chronically. Heavy episodic drinking, defined as consuming more than 60 grams of alcohol on at least one occasion in the past month, was reported by 10% of females and 24% of males aged 15 or over.

Regarding global alcohol intake, a downward trend has been observed. Total alcohol per capita consumption decreased from 5.7 liters in 2010 to 5.5 liters in 2019. The regions with the highest per capita consumption were regions of the Americas (7.5 liters) and Europe (9.2 liters). The prevalence of alcohol use

disorder worldwide decreased from 7.8% to 7% between 2010 and 2019 - this was due to a decrease in the Americas, Europe, and the Western Pacific, although there was an increase in the percentage in the African, Eastern Mediterranean, and Southeast Asia regions. [5]

A standard daily drink is typically defined as one containing 10 grams of pure alcohol. Regarding safe alcohol consumption levels, some evidence suggests that drinking below 100 grams of alcohol per week results in the lowest risk of mortality- potentially because of the positive impact on cardiovascular risk. [6] However, other studies suggest that the level of consumption that minimizes health risks is zero and alcohol should not be consumed at all. [7]

Prevalence of Alcohol-Induced Dementia

The development of dementia (referred to as "major neurocognitive disorder" in the DSM-5) is often prolonged and usually preceded by mild cognitive impairment (MCI, referred to as "mild neurocognitive impairment" in the DSM-5 and ICD-11). Both conditions are characterized by an objective deterioration of previous cognitive functions. Unlike dementia, MCI does not significantly interfere with everyday or social functioning- complex tasks may require greater effort to accomplish, but remain achievable. In contrast, cognitive impairments in dementia may make activities of daily living impossible to perform independently. Memory impairment is present in most cases of dementia, but not always. [8, 9]

The most common types of dementia include Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies and mixed dementia. Less common types include frontotemporal degeneration and dementias associated with brain injury, infections, and alcohol abuse. [8] Excessive alcohol consumption increases the risk of all types of dementia. [10]

Among Europeans aged 45-64, an average of 3.2% of dementia cases in women and 7.8% of dementia cases in men were attributed to high-risk alcohol use (defined as at least 24 grams of pure alcohol per day or 168 grams of pure alcohol per week). [11]

Dementia caused by alcohol differs slightly from other types of dementia as it affects men more often and has an earlier age of onset. [12] The clinical presentation also shows some differences. In Alzheimer's disease, patients had problems with naming, recognition memory, animal fluency and orientation, whereas patients with alcohol-related dementia suffered from fine motor control loss, and struggled with initial letter fluency and free recalling. [13]

Due to complex, diverse, and often coexisting mechanisms through which alcohol damages the brain, there is uncertainty regarding the classification and diagnosis of alcohol dementia as an isolated disease entity [14]. Clinicians sometimes use a broader term: "Alcohol-Related Brain Damage" (ARBD) to refer to several conditions, including alcohol-related dementia, Wernicke-Korsakoff syndrome, alcohol-related brain injury and alcohol amnestic syndrome, because they share common features [15]. The DSM-5 classification distinguishes "severe or mild alcohol-induced neurocognitive disorders" [16], and the ICD-11 "dementia due to alcohol use". [9]

Alcohol Metabolism

Alcohol is absorbed in the duodenum, jejunum, and stomach. It is transported through tissues via passive diffusion, which depends on the concentration gradient across the membrane - the higher the alcohol concentration, the faster the absorption. Alcohol is primarily metabolized through oxidative pathways, involving alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and catalase. Firstly, ethanol is oxidized to acetaldehyde, which is then converted by aldehyde dehydrogenase (ALDH) to acetate. This compound is then either further oxidized to carbon dioxide (CO2) and eliminated, or converted to acetyl-CoA used in lipid and cholesterol biosynthesis. [17, 18] Oxidative metabolism is linked to the generation of reactive oxygen species (ROS), which present a risk of oxidative stress-induced tissue damage. The non-oxidative pathway contributes minimally to overall alcohol metabolism, but it produces biologically active metabolites-fatty acid ethyl esters (FAEEs) and phosphatidyl ethanol. [18]

Alcohol is mostly metabolized peripherally, 90% of its metabolism occurs in the liver (primarily by ADH and, to a lesser extent, CYP2E1), but it also occurs in the central nervous system. The brain contains three ethanol-oxidizing systems:

- Catalase (responsible for 60% of alcohol brain metabolism),
- Cytochrome P450 2E1 (20% alcohol brain metabolism),
- Alcohol Dehydrogenase isoenzymes, with low activity (20% alcohol brain metabolism).

Catalase oxidizes ethanol mainly in the aminergic neurons of the brainstem. [19] Despite the modest contribution of alcohol dehydrogenase in overall alcohol metabolism in the brain, a significant accumulation of acetaldehyde has been observed in ADH-rich areas, leading to regional neurotoxicity. ADH I, III, and IV isoforms are present in the human brain, with the highest activity observed in Purkinje cells in the cerebellum and cholinergic and aminergic neurons in the brainstem. [20] Although cerebral metabolism accounts only for a fraction of alcohol metabolism in the body, it plays a crucial role in aldehyde and ROS induced local neurotoxicity. [21]

Mechanisms of Alcohol Related Brain Damage (ARBD)

Alcohol abuse is destructive to the brain through complex mechanisms, including nutritional deficiencies, liver failure, and the direct neurotoxic effects of ethanol and its metabolites. [22] The pathophysiology underlying the development of cognitive impairment in patients with AUD is complex and not fully understood.

A significant role is attributed to Wernicke-Korsakoff syndrome, a condition caused by nutritional deficiencies (specifically thiamine). It shares numerous characteristics with dementia, which is the reason it is often discussed alongside alcohol-induced dementia.

Thiamine Deficiency

Chronic malnutrition, resulting from alcohol abuse or other causes, leads to thiamine deficiency. Thiamine (vitamin B1) is required for the proper functioning of the central nervous system (CNS) and must be obtained through the diet. It plays a critical role in metabolic processes, nerve conduction, and maintaining the structure of neurons. It is required for metabolism of carbohydrates (production of energy), lipids (production of myelin - a substance surrounding neuronal axons, important for impulse conduction), and amino acids (synthesis of neurotransmitters). [22, 23, 24]

Individuals with alcohol use disorder develop thiamine deficiency through several mechanisms. They often have an imbalanced diet, deficient in vitamins. Furthermore, alcohol inhibits intestinal absorption of thiamine. It also reduces the activity of enzymes responsible for phosphorylating thiamine into its active form - thiamine pyrophosphate, while simultaneously increasing the activity of thiamine degrading enzymes. [23]

Severe thiamine deficiency can cause the development of Wernicke-Korsakoff syndrome. It is divided into two clinical stages: Wernicke encephalopathy, acute, often reversible condition, manifesting in nervous system symptoms. If thiamine deficiency is left untreated, it may progress to Korsakoff syndrome, an irreversible state characterized by confabulation and amnesia. [22, 24]

Beyond alcohol-related dementia, thiamine deficiency may be a significant factor in Alzheimer's disease. Decreased glucose metabolism in the brain is observed in AD patients, and it serves as an important marker controlling the progression of the disease. Reduced glucose metabolism is closely associated with Alzheimer's disease, but the exact mechanism behind this phenomenon has not been clarified. Given the importance of thiamine in glucose metabolism, it has been further investigated. Patients with AD demonstrated a reduced activity of thiamine-dependent enzymes, leading to glucose deficiency. Notably, both WKS and AD patients suffer from similar memory impairments - specifically amnesia, both caused by frontal dysfunction. [24, 25]

Animal studies have demonstrated that thiamine deficiency increased plaque formation, tau phosphorylation, and memory impairment - all of which are symptoms characteristic to AD. [26] Studies conducted on mice supplementing benfotiamine (a thiamine derivative) demonstrated its potential to inhibit the formation of amyloid plaques and improve memory. [27] While these observations suggest that thiamine supplementation may have a beneficial effect on Alzheimer's Disease, clinical studies are inconsistent. Some studies report a slight positive impact of supplementation on cognitive function, whereas others fail to demonstrate significant effects. [24,25]

Oxidative Stress

Alcohol metabolism generates reactive oxygen species (ROS) and reactive nitrogen species (RNS), primarily through CYP2E1 pathways. Although the organism possesses defence mechanisms against free radicals, they are limited in the central nervous system. Excessive and chronic ethanol consumption leads to a pathological ROS overproduction coupled with antioxidant mechanisms insufficiency. This results in oxidative stress, which negatively impacts cells. ROS interact destructively with subcellular organelles: mitochondria, endoplasmic reticulum, and cellular macromolecules: proteins, lipids, and DNA [28, 29].

These processes negatively impact the blood-brain barrier (BBB), a semipermeable membrane responsible for regulation of the transport to and from the brain tissue. Free radicals, such as superoxide, and hydrogen peroxide (H2O2) trigger oxidative stress response, which increases inflammatory activation and leads to cytoskeletal destabilization of the BBB. [30]

Neuroinflammation

Certain brain-signaling molecules in the central nervous system, function as immune-signaling molecules peripherally. These include High-mobility group box 1 (HMGB1), Toll-like receptor 4 (TLR4), and various cytokines. In the brain, neurons, astrocytes, and microglia are responsible for the secretion and response to these neuroimmune factors. In a properly functioning brain, the immune system is inactive, with only microglia as the resident immune cell. However, external factors, such as binge drinking, lead to the induction of neuroimmune genes and microglial activation. Alcohol abuse results in an increase in:

- neuronal excitability,
- signaling in High-mobility group box 1 (HMGB1), Toll-like receptor 4 (TLR4), and NF-κB,
- levels of peripheral cytokines,
- oxidative stress.

Prolonged and progressive activation of neuroimmune pathways eventually lead to neurodegeneration (primarily involving frontal cortical regions) and impaired neurogenesis within the hippocampus. [31]

Acetaldehyde and Adduct Formation

Acetaldehyde, the primary metabolite of ethanol, easily binds to proteins to form adducts.

One of the targets of this process is tubulin. Physiologically, this protein forms the cytoskeleton of the cells, its functions include: maintaining cellular stability and shape, enabling vesicular transport (essential for neurotransmitter release) and coordinating cell division.

Post-mortem histological studies and protein profiling have revealed significant differences between chronic alcohol users and the control group. Specifically, a major α- and β-tubulin, as well as spectrin β-chain protein losses were observed in protein profiling of AUD individuals. These structural changes were most significant in the prefrontal cortex, and to a lesser extent were also present in the caudate nucleus, hippocampus, and cerebellum. [32] Given that the prefrontal cortex is responsible for working memory, abstract thinking, and decision-making, [33] the described changes may be linked to the cognitive impairments associated with chronic alcohol use.

NMDA Receptors Dysregulation

The N-methyl-D-aspartate (NMDA) receptors are integral for excitatory synaptic transmission, they regulate neuroplasticity and brain response to external stimuli - crucial factors for learning and memory. Chronic ethanol exposure decreases the amount of NMDA receptors while simultaneously upregulating their sensitivity. Additionally, the dysfunction of presynaptic neurotransmitter release results in a higher glutamate concentration, stimulating the NMDA receptors further. It can cause an increased influx of Ca2+ ions into the cells, activating apoptotic pathways and resulting in neuronal death. [34,35]

Given this mechanism, memantine- a non-competitive NMDA receptor antagonist, has been investigated as a potentially neuroprotective factor. A study involving a small group of patients with alcohol-related dementia has been conducted. For 12 weeks the participants were given memantine, gradually increased to a dose of 20 mg. Subjects demonstrated improvements in global cognition, reduction in behavioral symptoms, and increase in overall quality of life. [34]

Relationship Between Drinking Pattern and Dementia Risk

Numerous studies suggest a U-shaped or J-shaped correlation between cognitive functions and alcohol consumption. It indicates that low-to-moderate drinking may have a protective effect against the development of cognitive impairment compared to both abstainers and heavy drinkers. [4, 10, 36, 37]

A comprehensive 2025 meta-analysis, which synthesized clinical trials from 1992 to 2024, involving over 24 million participants (aged 50-79), from across Europe, North America, and Asia, further confirms this relationship. The results obtained were as follows:

• Light-to-moderate drinking (defined as <3 drinks per day or <49.9 g of ethanol per day) was associated with a reduced risk of all-cause dementia (RR = 0.88, 95% CI: 0.81-0.96) and Alzheimer's disease,

though effect on vascular dementia was not significant. This neuroprotective effect is observed particularly in the European population aged between 60 and 69.

- Heavy alcohol consumption (≥3 drinks per day or ≥50 g of ethanol per day) significantly increased the risk of every type of dementia, for all-cause dementia (RR = 1.18, 95% CI: 1.02-1.36).
- Alcohol Use Disorder (defined as long-term hazardous alcohol intake or alcohol dependence) drastically increased the risk of all-cause dementia (RR = 3.35, 95% CI: 3.29-3.42) [10].

Non-drinkers group

A debate surrounding worse results among abstainers sometimes suggests that an underlying cause may be a failure in distinguishing life-long abstainers from former drinkers who have abused alcohol in the past. In this case, prior alcohol consumption would have a negative impact on the brain, persisting despite current abstinence [8, 10, 11, 38]. However, a meta-analysis that strictly isolated life-long abstainers still observed the protective effect of light alcohol consumption [10]. Other studies found that former alcohol use demonstrated no significant difference when compared to life-long abstinence in regards of relative dementia risk [4].

Heavy Drinkers and AUD

Individuals who consume alcohol excessively are the most at risk for its negative effects. [8, 10, 37, 38]. Chronic heavy alcohol use, as well as irregular heavy drinking, compared to moderate drinking are linked to a higher risk of developing cognitive impairment and dementia- both clinically and in neuroimaging [8, 37] It should be noted that in some studies, the effect of heavy drinking on the development of dementia was not significant and did not demonstrate a negative effect [39, 40]. Age of the participants may play an important role - amongst individuals 65 and over, heavy alcohol use seems to not change the risk of dementia, whereas in individuals aged between 45 and 65 it elevates it. [11]

In AUD participants the hazard ratio for dementia is estimated to range between 2.73 and 4.6, depending on the study. [10, 11, 41]. Higher risk affects all-cause dementia, as well as Alzheimer's disease and vascular dementia. [41]

The Role of Baseline Cognitive Status

A research examining a group of people over 72 years of age, found that the baseline Mild Cognitive Impairments (MCI) may be important.

1. In the group of individuals previously not presenting MCI: less than one drink per week demonstrated a protective effect. It reduced the risk of dementia when compared to infrequent, higher-quantity drinkers and abstainers.
2. In individuals with pre-existing MCI: no such association was observed. Excessive drinking (over 14.0 drinks per week) significantly increased the hazard ratio of dementia. [38]

Alcohol Consumption and Brain Atrophy In Neuroimaging

While it is suggested that consuming low-to-moderate alcohol quantities may decrease the risk of developing dementia, studies regarding brain structure demonstrate negative consequences of doing so. Isolated studies have reported either no significant effect on brain volume [42] or a potentially beneficial effect of wine consumption on total brain volume [43], but the vast majority of evidence indicate otherwise- that even small amounts of alcohol cause atrophy and brain volume reduction. [44, 45, 46, 47]

Initial hypothesis regarding positive effects of moderate alcohol consumption focused on its potential to reduce the incidence of cerebral infarction and white matter lesions in MRI scans. However, a study examining such dependence failed to demonstrate that effect. Conversely, it was found that even moderate alcohol consumption correlates with brain changes - an increase in both ventricular size and sulcal size [44] and a decrease in adjusted total brain volume (aTBV) [45]. Changes were proportional to the amount of alcohol consumed per week.

Structural brain differences are observable even at low-to-moderate consumption levels (56-112g per week), compared to individuals consuming less than 56g per week. These differences include gray matter volumes reduction, while higher consumption levels are further associated with changes in white matter microstructure. [46]

Atrophy involves the frontal, temporal, parietal, and occipital lobes, as well as structures such as the insula, cingulate, hippocampus, amygdala, putamen, nucleus accumbens, thalamus, cerebellum, and brain stem. While observed changes occur similarly in both sexes; some data suggest that women may experience a higher

degree of global brain atrophy, except for the amygdala, which shows more pronounced volume reduction in men. [47]

Changes were evident in elderly and middle-aged population, as well as in adolescents. [47] Adolescents reporting higher alcohol intake exhibit reduced gray matter volume and detectable white matter alterations compared to their non-drinking peers. [47, 48] Furthermore, fMRI scans revealed different patterns of brain activity in this group. These changes were more significant among females. [48]

Brain structure alterations are substantially more severe in individuals with AUD, characterized by reductions in the volume of the cortex, subcortex, and limbic structures. In these cases, brain destruction is caused by many factors – beyond the neurotoxic effects of ethanol on the brain, indirect factors play a crucial role. These include an increased risk of strokes, seizures and brain trauma, as well as organ dysfunction, malnutrition, and thiamine deficiency. In cases of alcohol-related dementia, the most profound damage is typically observed in the frontal lobes. [49]

Abstinence and Neurological Recovery

Maintenance of abstinence is critical for the restoration of physiological functioning. CT scans of chronic alcoholics (without Wernicke-Korsakoff syndrome) have demonstrated an increase in cerebral blood flow as well as total brain volume, both previously reduced by the toxic effects of alcohol and recovered due to abstinence. [50] This recovery typically occurs within weeks or months of abstinence. However, total baseline brain volume is not fully restored, as the recovery is only partial. [49]

Clinical improvement is also noticeable. Individuals diagnosed with AUD, who sustained 6-12 months of abstinence showed improvement in nearly all neuropsychological functions, including memory, decision-making, and attention. [51]

Conclusions

Alcohol consumption is a significant risk factor for the development of dementia and its effects are dose-dependent. Low-to-moderate alcohol consumption has been associated with a reduced risk, while high consumption increases the risk of dementia. These intriguing mechanisms are not fully understood and should be the subject of further clinical research.

Alcohol exerts neurotoxic effects through multiple mechanisms. These include oxidative stress, neuroinflammation, acetaldehyde toxicity, thiamine deficiency, and impaired neurotransmission. The entire brain is affected, but damage to the prefrontal and frontal lobes is often specifically identified - which may be correlated with cognitive impairment and dementia. Partial recovery of brain volume and clinical improvement is possible through continued abstinence.

Given the prevalence of alcohol consumption and the predicted increase in dementia, it is important to understand and counteract the negative effects of alcohol consumption as thoroughly as possible. Further research is needed to understand the precise relationship between drinking patterns and cognitive decline and to develop the most effective prevention and treatment strategies.

Author's contribution:

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REFERENCES

1. Prince, M., Albanese, E., Guerchet, M., & Prina, M. (2014). *World Alzheimer report 2014: Dementia and risk reduction: An analysis of protective and modifiable factors*. Alzheimer's Disease International.
2. World Health Organization. (2017). *Global action plan on the public health response to dementia 2017–2025*. https://www.who.int/publications/i/item/global-action-plan-on-the-public-health-response-to-dementia-2017---2025
3. United Nations, Department of Economic and Social Affairs, Population Division. (2020). *World population ageing 2019* (ST/ESA/SER.A/444). United Nations.
4. Mewton, L., Visontay, R., Hoy, N., Lipnicki, D. M., Sunderland, M., Lipton, R. B., Guerchet, M., Ritchie, K., Najar, J., Scarmeas, N., Kim, K. W., Riedel-Heller, S., van Boxtel, M., Jacobsen, E., Brodaty, H., Anstey, K. J., Haan, M., Scazufca, M., Lobo, E., . . . COSMIC Collaborators. (2024). The relationship between alcohol use and dementia in adults aged more than 60 years: A combined analysis of prospective, individual-participant data from 15 international studies. *Addiction, 118*(3), 412–424. https://doi.org/10.1111/add.16035
5. World Health Organization. (2024). *Global status report on alcohol and health and treatment of substance use disorders*. https://www.who.int/publications/i/item/9789240096745
6. Wood, A., Kaptoge, S., Butterworth, A., et al. (2018). Risk thresholds for alcohol consumption: Combined analysis of individual-participant data for 599,912 current drinkers in 83 prospective studies. *The Lancet, 391*(10129), 1513–1523. https://doi.org/10.1016/S0140-6736(18)30134-X
7. Griswold, M., Fullman, N., Hawley, C., et al. (2018). Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet, 392*(10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2
8. Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., Brayne, C., Fox, N. C., Ferri, C. P., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Nakasujja, N., Rockwood, K., . . . Mukadam, N. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet Standing Commission. *The Lancet, 404*, 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0
9. World Health Organization. (2026). *International classification of diseases* (11th rev.): Neurocognitive disorders. https://icd.who.int/browse/2026-01/mms/en#195531803
10. Zhang, R., Li, B., & Miao, Y. (2025). Alcohol consumption and risk of dementia: A systematic review and meta-analysis. *Internal Medicine Journal*. Advance online publication. https://doi.org/10.1111/imj.70288
11. Kilian, C., Klinger, S., Rehm, J., & Manthey, J. (2023). Alcohol use, dementia risk, and sex: A systematic review and assessment of alcohol-attributable dementia cases in Europe. *BMC Geriatrics, 23*(1), Article 246. https://doi.org/10.1186/s12877-023-03972-5
12. Draper, B., Karmel, R., Gibson, D., Peut, A., & Anderson, P. (2011). Alcohol-related cognitive impairment in New South Wales hospital patients aged 50 years and over. *The Australian and New Zealand Journal of Psychiatry, 45*(11), 985–992. https://doi.org/10.3109/00048674.2011.610297
13. Saxton, J., Munro, C. A., Butters, M. A., Schramke, C., & McNeil, M. A. (2000). Alcohol, dementia, and Alzheimer's disease: Comparison of neuropsychological profiles. *Journal of Geriatric Psychiatry and Neurology, 13*(3), 141–149. https://doi.org/10.1177/089198870001300308
14. Moriyama, Y., Mimura, M., Kato, M., & Kashima, H. (2006). Primary alcoholic dementia and alcohol-related dementia. *Psychogeriatrics, 6*, 114–118. https://doi.org/10.1111/j.1479-8301.2006.00168.x
15. Aziz, V. M. (2014). Alcohol-related brain damage (ARBD): A service need. *International Psychogeriatrics, 26*(10), 1747–1749. https://doi.org/10.1017/S1041610214001252
16. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596
17. Cederbaum, A. I. (2012). Alcohol metabolism. *Clinics in Liver Disease, 16*(4), 667–685. https://doi.org/10.1016/j.cld.2012.08.002
18. Zakhari, S. (2006). Overview: How is alcohol metabolized by the body? *Alcohol Research & Health, 29*(4), 245–254.
19. Dyr, W., & Wyszogrodzka, E. (2018). The importance of acetaldehyde in the metabolism and mechanism of ethyl alcohol action. *Alcoholism and Drug Addiction, 31*(4), 301–314. https://doi.org/10.5114/ain.2018.83913
20. Jelski, W., Grochowska-Skiba, B., & Szmitkowski, M. (2007). Dehydrogenaza alkoholowa i metabolizm alkoholu etylowego w mózgu. *Postępy Higieny i Medycyny Doświadczalnej, 61*, 226–230.
21. Gołaszewski, P., Wawrzyniak, A., Kłosowicz, M., Burbelka, A., & Balawender, K. (2025). Neurotoxicity of chronic alcohol exposure: Mechanistic insights, cellular disruption, and emerging therapeutic strategies. *International Journal of Molecular Sciences, 27*(1), Article 299. https://doi.org/10.3390/ijms27010299
22. Zahr, N. M., Kaufman, K. L., & Harper, C. G. (2011). Clinical and pathological features of alcohol-related brain damage. *Nature Reviews Neurology, 7*(5), 284–294. https://doi.org/10.1038/nrneurol.2011.42
23. Langlais, P. J. (1995). Alcohol-related thiamine deficiency: Impact on cognitive and memory functioning. *Alcohol Health and Research World, 19*(2), 113–121.

24. Gibson, G. E., Hirsch, J. A., Fonzetti, P., Jordan, B. D., Cirio, R. T., & Elder, J. (2016). Vitamin B1 (thiamine) and dementia. *Annals of the New York Academy of Sciences, 1367*(1), 21–30. https://doi.org/10.1111/nyas.13031
25. Gibson, G. E., Hirsch, J. A., Cirio, R. T., Jordan, B. D., Fonzetti, P., & Elder, J. (2013). Abnormal thiamine-dependent processes in Alzheimer's disease: Lessons from diabetes. *Molecular and Cellular Neuroscience, 55*, 17–25. https://doi.org/10.1016/j.mcn.2012.09.001
26. Karuppagounder, S. S., Xu, H., Shi, Q., Chen, L. H., Pedrini, S., Pechman, D., Baker, H., Beal, M. F., Gandy, S. E., & Gibson, G. E. (2009). Thiamine deficiency induces oxidative stress and exacerbates the plaque pathology in Alzheimer's mouse model. *Neurobiology of Aging, 30*(10), 1587–1600. https://doi.org/10.1016/j.neurobiolaging.2007.12.013
27. Pan, X., Gong, N., Zhao, J., Yu, Z., Gu, F., Chen, J., Sun, X., Zhao, L., Yu, M., Xu, Z., Dong, W., Qin, Y., Fei, G., Zhong, C., & Xu, T. L. (2010). Powerful beneficial effects of benfotiamine on cognitive impairment and beta-amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice. *Brain, 133*(Pt. 5), 1342–1351. https://doi.org/10.1093/brain/awq069
28. Ruiter-Lopez, L., Khan, M. A. S., Wang, X., & Song, B.-J. (2025). Roles of oxidative stress and autophagy in alcohol-mediated brain damage. *Antioxidants, 14*(3), Article 302. https://doi.org/10.3390/antiox14030302
29. Wu, D., & Cederbaum, A. I. (2003). Alcohol, oxidative stress, and free radical damage. *Alcohol Research & Health, 27*(4), 277–284.
30. Pervin, Z., & Stephen, J. M. (2021). Effect of alcohol on the central nervous system to develop neurological disorder: Pathophysiological and lifestyle modulation can be potential therapeutic options for alcohol-induced neurotoxication. *AIMS Neuroscience, 8*(3), 390–413. https://doi.org/10.3934/Neuroscience.2021021
31. Crews, F. T., Sarkar, D. K., Qin, L., Zou, J., Boyadjieva, N., & Vetreno, R. P. (2015). Neuroimmune function and the consequences of alcohol exposure. *Alcohol Research: Current Reviews, 37*(2), 331–351. https://doi.org/10.35946/arcr.v37.2.15
32. Erdozain, A. M., Morentin, B., Bedford, L., King, E., Tooth, D., Brewer, C., Wayne, D., Johnson, L., Gerdes, H. K., Wigmore, P., Callado, L. F., & Carter, W. G. (2014). Alcohol-related brain damage in humans. *PLOS ONE, 9*(4), Article e93586. https://doi.org/10.1371/journal.pone.0093586
33. Chafee, M. V., & Heilbronner, S. R. (2022). Prefrontal cortex. *Current Biology, 32*(8), R346–R351. https://doi.org/10.1016/j.cub.2022.02.071
34. Cheon, Y., Park, J., Joe, K. H., & Kim, D. J. (2008). The effect of 12-week open-label memantine treatment on cognitive function improvement in patients with alcohol-related dementia. *The International Journal of Neuropsychopharmacology, 11*(7), 971–983. https://doi.org/10.1017/S1461145708008663
35. Chandrasekar, R. (2013). Alcohol and NMDA receptor: Current research and future direction. *Frontiers in Molecular Neuroscience, 6*, Article 14. https://doi.org/10.3389/fnmol.2013.00014
36. Kim, J. W., Lee, D. Y., Lee, B. C., Jung, M. H., Kim, H., Choi, Y. S., & Choi, I. G. (2012). Alcohol and cognition in the elderly: A review. *Psychiatry Investigation, 9*(1), 8–16. https://doi.org/10.4306/pi.2012.9.1.8
37. Rehm, J., Hasan, O. S. M., Black, S. E., Shield, K. D., & Schwarzinger, M. (2019). Alcohol use and dementia: A systematic scoping review. *Alzheimer's Research & Therapy, 11*(1), Article 1. https://doi.org/10.1186/s13195-018-0453-0
38. Koch, M., Fitzpatrick, A. L., Rapp, S. R., Nahin, R. L., Williamson, J. D., Lopez, O. L., DeKosky, S. T., Kuller, L. H., Mackey, R. H., Mukamal, K. J., Jensen, M. K., & Sink, K. M. (2019). Alcohol consumption and risk of dementia and cognitive decline among older adults with or without mild cognitive impairment. *JAMA Network Open, 2*(9), Article e1910319. https://doi.org/10.1001/jamanetworkopen.2019.10319
39. Chen, Y., Yin, X., Wang, X., Zheng, X., Yang, X., Zhou, J., Shi, M., & Zhang, Y. (2025). Associations of alcohol drinking with incident dementia: A prospective study from the UK Biobank. *European Journal of Epidemiology, 40*(11), 1345–1354. https://doi.org/10.1007/s10654-025-01304-y
40. Anstey, K. J., Mack, H. A., & Cherbuin, N. (2009). Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. *The American Journal of Geriatric Psychiatry, 17*(7), 542–555. https://doi.org/10.1097/JGP.0b013e3181a2fd07
41. Zhao, S., Widman, L., Hagström, H., & Shang, Y. (2024). Disentangling the contributions of alcohol use disorder and alcohol-related liver disease towards dementia: A population-based cohort study. *Addiction, 119*(4), 706–716. https://doi.org/10.1111/add.16395
42. Davis, B. J., Vidal, J. S., Garcia, M., Aspelund, T., van Buchem, M. A., Jonsdottir, M. K., Sigurdsson, S., Harris, T. B., Gudnason, V., & Launer, L. J. (2014). The alcohol paradox: Light-to-moderate alcohol consumption, cognitive function, and brain volume. *The Journals of Gerontology: Series A, 69*(12), 1528–1535. https://doi.org/10.1093/gerona/glu092
43. Gu, Y., Scarmeas, N., Short, E. E., Luchsinger, J. A., DeCarli, C., Stern, Y., Manly, J. J., Schupf, N., Mayeux, R., & Brickman, A. M. (2014). Alcohol intake and brain structure in a multiethnic elderly cohort. *Clinical Nutrition, 33*(4), 662–667. https://doi.org/10.1016/j.clnu.2013.08.004
44. Ding, J., Eigenbrodt, M. L., Mosley, T. H., Jr., Hutchinson, R. G., Folsom, A. R., Harris, T. B., & Nieto, F. J. (2004). Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) study. *Stroke, 35*(1), 16–21. https://doi.org/10.1161/01.STR.0000105929.88691.8E

45. Immonen, S., Launes, J., Järvinen, I., Virta, M., Vanninen, R., Schiavone, N., Lehto, E., Tuulio-Henriksson, A., Lipsanen, J., Michelsson, K., & Hokkanen, L. (2020). Moderate alcohol use is associated with decreased brain volume in early middle age in both sexes. *Scientific Reports, 10*(1), Article 13998. https://doi.org/10.1038/s41598-020-70910-5
46. Topiwala, A., Ebmeier, K. P., Maullin-Sapey, T., & Nichols, T. E. (2022). Alcohol consumption and MRI markers of brain structure and function: Cohort study of 25,378 UK Biobank participants. *NeuroImage: Clinical, 35*, Article 103066. https://doi.org/10.1016/j.nicl.2022.103066
47. Karoly, H. C., Kirk-Provencher, K. T., Schacht, J. P., & Gowin, J. L. (2024). Alcohol and brain structure across the lifespan: A systematic review of large-scale neuroimaging studies. *Addiction Biology, 29*(9), Article e13439. https://doi.org/10.1111/adb.13439
48. Ewing, S. W., Sakhardande, A., & Blakemore, S. J. (2014). The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth. *NeuroImage: Clinical, 5*, 420–437. https://doi.org/10.1016/j.nicl.2014.06.011
49. Zahr, N. M. (2014). Structural and microstructural imaging of the brain in alcohol use disorders. *Handbook of Clinical Neurology, 125*, 275–290. https://doi.org/10.1016/B978-0-444-62619-6.00017-3
50. Ishikawa, Y., Meyer, J. S., Tanahashi, N., Hata, T., Velez, M., Fann, W. E., Kandula, P., Motel, K. F., & Rogers, R. L. (1986). Abstinence improves cerebral perfusion and brain volume in alcoholic neurotoxicity without Wernicke-Korsakoff syndrome. *Journal of Cerebral Blood Flow & Metabolism, 6*(1), 86–94. https://doi.org/10.1038/jcbfm.1986.11
51. Powell, A., Sumnall, H., Smith, J., Kuiper, R., & Montgomery, C. (2024). Recovery of neuropsychological function following abstinence from alcohol in adults diagnosed with an alcohol use disorder: Systematic review of longitudinal studies. *PLOS ONE, 19*(1), Article e0296043. https://doi.org/10.1371/journal.pone.0296043