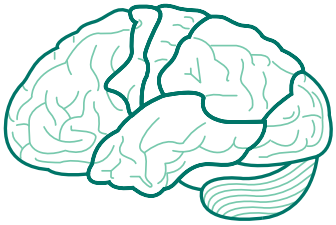
DRINKING AND COGNITIVE FUNCTION



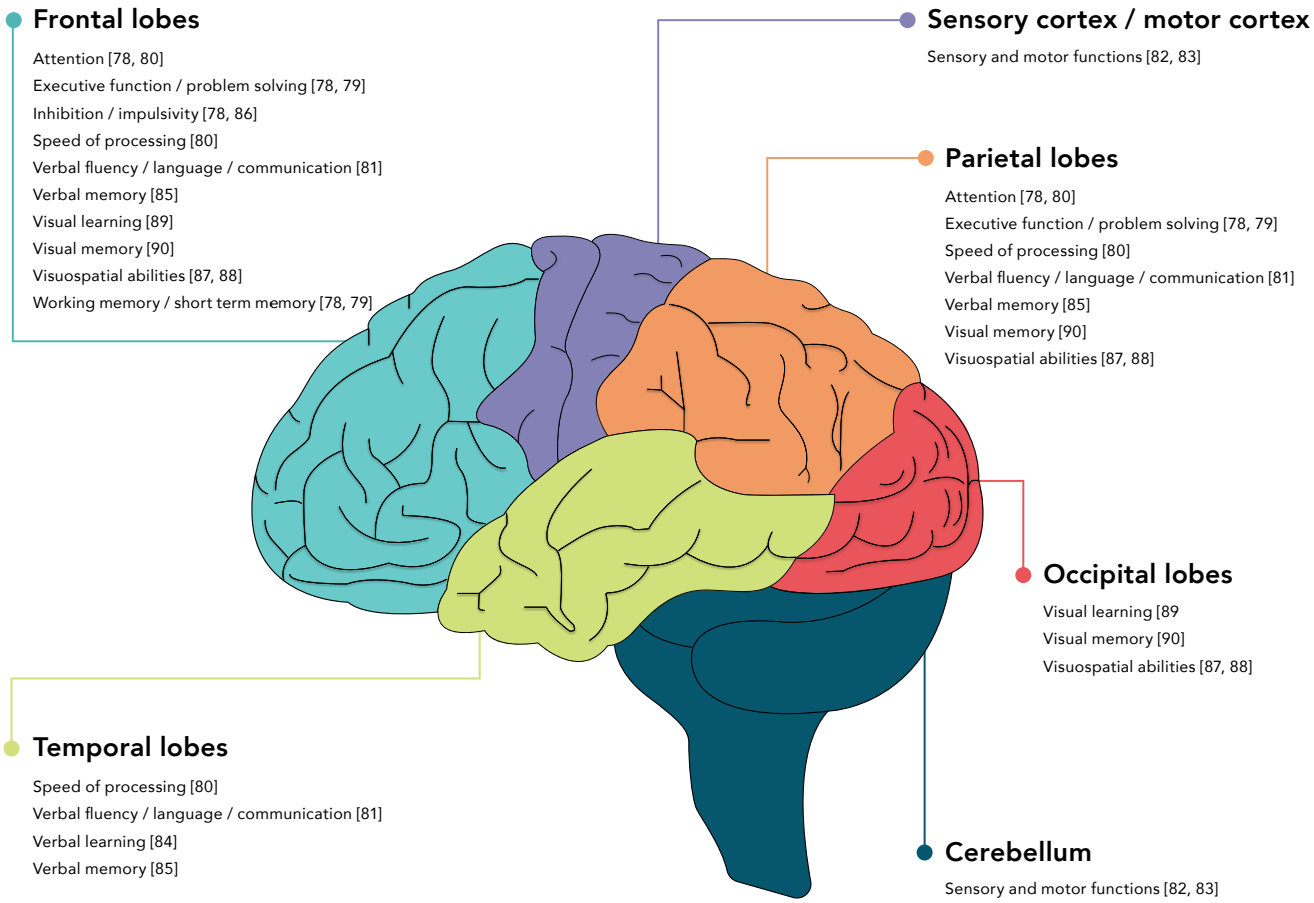
IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. The reviews report the findings of the referenced studies and are not intended to provide advice or recommendations. They do not necessarily reflect the views of IARD or its sponsoring companies.

Last Reviewed: **November 2019**

Background

Cognitive functions are processes that work together to enable our brains to manage information and perform tasks, including speech and movement. They comprise twelve domains, which are controlled by different areas of the brain.

Figure 1: Different areas of the brain manage and support 12 cognitive domains



These domains work together to support healthy cognitive function. They rely on *nerve cells* passing electrical signals to communicate with each other. However, certain chemicals can influence the speed and direction of these signals through the brain and the rest of the body. For example, alcohol acts as a depressant on some nerve cells; it reduces the frequency and speed of these signals, which may alter certain cognitive functions, such as speech and balance.

Risk factors for a decline in cognitive function vary and can overlap with different *neurodegenerative diseases,* such as Alzheimer's disease and Parkinson's disease. *Cognitive decline* specifically involves memory loss and problems with learning; in comparison, *neurodegeneration* is clinically-observed nerve loss. The Alzheimer's Association cites research by Baumgart et al. (2015) that indicates some modifiable risk factors include alcohol consumption, educational attainment, and other behavioral choices such as smoking, diet, and physical activity. Overall, the greatest risk factors for cognitive decline are non-modifiable: age and genetics [1].

This review discusses the role of alcohol as a risk factor for normal age-related decline. It also provides an overview of the available evidence on the role of alcohol as a risk factor for chronic cognitive impairment characterized by certain diseases, including alcohol-related brain damage (ARBD), dementia, Alzheimer's disease, Parkinson's disease, and Wernicke-Korsakoff syndrome. The associated delays in cognitive and motor function development as a result of prenatal alcohol exposure are covered in **IARD'S Review of Fetal Alcohol Spectrum Disorders** and therefore will not covered in this review.

This Health Review presents the findings from meta-analyses, systematic reviews, large prospective cohort and case-control studies from the past 10 years (2008–2018) on alcohol's effect on cognitive decline. We give priority to the results of meta-analyses and pooled cohort studies over presenting the results of individual studies, when possible. Where there is limited research available, we may include the results from individual studies and studies pre-dating the prior 10-year timeframe. The conditions and outcomes described in this review reflect those areas where there is a sufficient body of research on the association between alcohol consumption and cognitive function that could be considered more developed than exploratory research.

A glossary of key terms appears on page 9
Additional information appears on page 10

Summary of recent research

DRINKING LEVELS AND COGNITIVE DECLINE

Light, moderate, and heavy drinking definitions
There are no universally-accepted definitions for drinking levels. This is evident in the wide variation between national guidelines, as well as differences in standard national drink sizes. Many research studies refer to an assumed standard drink or to drinking levels associated with guidelines. The terms light, moderate, and heavy drinking – as defined by the studies included in this Health Review – vary widely in their definitions. For example, moderate drinking can refer to one to two drinks per day, one drink for women and two drinks for men per day; it can also refer to 12.5 to 25g of pure alcohol consumed per day, 10 to 20g per day, or up to 24g per day.

When describing the results of specific studies, this Health Review reports the drinking level information provided by the referenced study. When describing overall results across several studies, this Health Review may use light or moderate drinking to broadly indicate less than, or up to, one to two drinks per day, and may use heavy drinking to broadly indicate more than two or three drinks per day.

Heavy consumption: Heavy alcohol consumption sustained over many years may affect cognitive decline [2, 3].

- Long-term heavy alcohol consumption can cause neurodegeneration, specifically in the cortex [4] and *hippocampus* [5].

- Studies using *magnetic resonance imaging (MRI)* have found that heavier drinking patterns are associated with decreased *grey matter, white matter,* and hippocampal density; these are the tissues that support memory and learning [6-8].

Light-to-moderate consumption. As described in a recent scoping review [9], the impact of alcohol consumption on cognitive decline demonstrates that low-to-moderate drinking is associated with a lower risk of cognitive decline, relative to abstinence [10], whereas heavy and binge drinking [9, 11] are associated with a higher risk of cognitive decline.

- While several studies have found that low-to-moderate consumption is associated with lower risk of cognitive decline, some research has found that moderate drinking, starting with 8-16g/day, was associated with a small but significantly greater decline in lexical fluency, but not semantic fluency or word recall, compared with nondrinkers [6].

Moderate drinking has also been associated with a reduced risk for all-cause dementia and Alzheimer's dementia, as reported in a 2017 systematic review and meta-analysis [12].

- The association between drinking and risk of dementia may be different for men and women [13], and the difference may not be solely explained by men's higher average-drinking levels [14].

EFFECTS OF AGING AND ALCOHOL ON THE BRAIN

Older populations: Cognitive decline most commonly affects older populations [15-18].

- Evidence suggests that light-to-moderate drinking may reduce the risk of dementia in old age, a finding that appears consistent for both infrequent and frequent drinkers [19].
- Studies that focus on adults who live in retirement communities have found that moderate drinking was more likely to be associated with survival up to the age of 85 years without cognitive decline [20], and with better visual memory retention [21], than abstention.
- Findings on the association between drinking levels and cognitive decline have been mixed. Some studies show no protective effect on cognitive decline among light drinkers, but show evidence of a greater risk of decline among heavy drinkers [6].
- Other studies show gender-specific differences that demonstrate that moderate drinking may have a protective effect for women but no significant association for men [22].

Neurodegeneration involves the loss of *neurons* or nerve function, inducing brain changes that are associated with some cognitive decline, such as problems with memory or *executive function*. Premature cognitive decline can occur as an acute impairment following an injury or from long-term exposure to a risk factor. However, neurodegenerative diseases are primarily an issue for the elderly population [23]; these diseases are characterized by a progressive decline in cognitive domains.

The following common neurodegenerative diseases share many of the same risk factors [24]:

- Dementia [25]
- Parkinson's disease [26]
- Alzheimer's disease [27]

Dementia: Thirteen studies in the past 10 years have examined the association between alcohol and the risk of dementia. Dementia diagnosis is a predictor of steeper cognitive decline in domains such as memory, executive function, processing speed, and global cognitive function for both men and women [28]. This neurodegenerative disease is characterized by a loss of cognitive functioning skills including memory, language skills, visual perception, and problem solving.

- Seven of these studies have found that light-to-moderate drinkers had a lower risk for dementia, compared to abstainers [12, 19, 29-33]. Two of these studies also found an increased risk for heavy drinkers [32, 33].
- A recent retrospective analysis of over 30 million people in France showed that having an alcohol use disorder (AUD) was a significant modifiable risk factor for dementia among men and women aged over 65 years. The study also showed that over half of those with early-onset dementia (individuals that are afflicted under the age of 65) had a history of alcohol problems [34].

- Research indicates that having an alcohol use disorder could be linked to an increase in inflammation brought on by long-term heavy drinking [35]; this inflammation has been linked to dementia [36].

- Alcohol-induced dementia can occur before the age of 65 years [34], although research indicates that this type of cognitive impairment can potentially be reversed with alcohol abstinence [37, 38].

Parkinson's disease: Four studies in the past 10 years have examined the association between alcohol consumption and the risk of Parkinson's disease, which is a neurodegenerative disease characterized by difficulties with memory retrieval, executive function, motor function, and attention.

- Some studies found that regular, low-volume alcohol consumption reduced the risk of Parkinson's disease [39, 40], and a meta-analysis found that compared to no or light alcohol consumption, heavy or moderate alcohol consumption had a reduced risk for Parkinson's disease [41].

- A Swedish national cohort study found that diagnosis of an alcohol use disorder was associated with a high risk of Parkinson's disease, particularly among adults younger than 44 years who had been hospitalized with a diagnosis of Parkinson's prior to, or concurrent with, admission for an alcohol use disorder [42].

Alzheimer's disease: Two large studies in the past 10 years have examined the association between alcohol and Alzheimer's disease. This neurodegenerative disease is characterized by progressive cognitive decline, usually involving memory loss and difficulties understanding and producing speech.

- One study confirmed that heavy drinking increased the rate of decline among Alzheimer's disease patients, compared to abstaining and mild-to-moderate drinking [43].

- A large systematic review found that low-to-moderate alcohol consumption was associated with a 32% reduced risk of Alzheimer's disease, compared to abstainers [19].

Middle age: Neurodegeneration symptoms usually become apparent between the ages of 40 and 64 years [11, 44].

- Heavy alcohol consumption among people aged an average of 55 years old was associated with impairment of some executive function components at 72 years old, such as lower *verbal fluency* [45].

- Another study showed that moderate drinkers had larger hippocampal volume and light drinkers had better *episodic memory* recall, compared to lifelong abstainers [46].

Adolescents: Alcohol consumption in adolescence can affect short-term and longer-term cognitive function [47, 48]. Excessive alcohol use during "critical adolescent developmental stages" [49] or "windows of vulnerability" [50] may make young people more susceptible to alcohol-induced impairments [3, 51], including memory retrieval [52], attention, cognitive processing, and language skills [50]. These sometimes subtle cognitive changes can rapidly deteriorate cognitive functions as the brain reaches maturation, leading to irreversible brain damage [48].

- Studies focusing on adolescents have shown reductions in left-hippocampal volumes among drinkers compared to nondrinkers, [53] and hippocampal asymmetry among those with AUD symptoms [53, 54]. These reductions may impair visual and verbal memory performance.

ALCOHOL-SPECIFIC NEURODEGENERATIVE DISORDERS

These diseases are characterized by long-term heavy alcohol consumption and cognitive decline that cannot be better explained by another neurodegenerative diagnosis [55].

Alcohol-related brain damage (ARBD): ARBD is characterized by brain damage [7, 56] caused by long-term heavy alcohol consumption [57].

- Research indicates that ARBD typically affects individuals aged in their 40s and 50s, with women commonly presenting symptoms a decade earlier than men [58].

- Some people with ARBD make a partial or full recovery [59], but symptoms can still persist after abstinence from alcohol [60].

Wernicke-Korsakoff syndrome: This neurodegenerative disease is caused by a vitamin B1 (thiamine) deficiency [38], and is characterized by an acute onset of short-term memory loss [61], loss of coordination, abnormal eye movements, confusion, and memory impairment [62].

- Heavy and prolonged alcohol consumption can cause thiamine deficiency by compromising normal thiamine absorption or reducing thiamine storage capability sustained by an alcohol use disorder [63, 64].

    - Acute thiamine deficiency can result in the brain disease *Wernicke encephalopathy*, which causes brain lesions and is one of the leading risk factors associated with this disease. If left untreated, Wernicke's encephalopathy can lead to Korsakoff's syndrome [38, 65]: a severe neurodegenerative disorder characterized by an inability to create new memories [66].

- Wernicke encephalopathy can be treated with rapid thiamine treatment [63, 67].

OTHER RISK FACTORS

Research suggests that alcohol consumption can worsen the risk of cognitive decline among people with cardiovascular or mental health conditions [3].

- Cardiovascular disease has been found to be associated with a decline in cognitive domains over time, including language, attention, executive function, and psychomotor speed [68].

    - *Cardiometabolic diseases*, including both cardiovascular disease and diabetes, appear to explain some of the increased risk for dementia among alcohol abstainers [33].

    - Stroke and hypertension diagnoses were found to be strong predictors for early onset dementia [69].

- Depression has consistently been associated with faster cognitive decline [28, 69-72].

Methodological issues

Cognitive impairment assessments: The use of different cognitive assessment tests to measure and assess various components of cognitive function makes it hard to compare results across different studies.

A study subject's comprehension of the assessment tasks and their motivation to perform well on cognition tests presents the following issues:

- Floor effects: these occur when study participants score poorly, perhaps as a result of an assessment being too difficult.
- Ceiling effects: these occur when study participants score better than expected, perhaps as a result of an assessment being too easy.
- Practice effects: test results can be influenced if subjects complete an assessment more than once [6, 28, 73].

Other methodological issues inherent in observational study designs include classification errors, selection bias, and residual confounding.

Classification errors: The way in which drinkers and nondrinkers are classified across studies and countries may have an impact on observed outcomes for cognitive decline [19]. The "sick quitter" hypothesis was first described in 1988 and suggests that many former drinkers have stopped drinking for health reasons [74]. If these individuals are classified as nondrinkers in the same group as lifetime abstainers, then any existing poor health conditions may make it appear that abstainers are at higher risk of cognitive decline than moderate drinkers.

- A meta-analysis suggested that the results reported may be confounded by the inclusion of former drinkers in the abstainer or non-drinker category [30].
- Some studies omit all abstainers from their analysis to reduce the "sick quitter" effect [16, 75]. However, this would not eliminate unhealthy individuals in the reference group because those who become ill may just reduce their consumption instead of stopping drinking completely [75].

Selection bias: Selection bias may occur when individuals participating in a research study are not representative of the general or targeted population, and may result in a distortion (underestimation or overestimation) of the relationship between alcohol consumption and cognitive decline. Another type of selection bias relates to survival bias: the unavailability of drinkers who have died prematurely from an alcohol-related cause, for participation in a research study. This bias assumes that individuals who die at younger ages are more likely to be drinkers than non-drinkers, because alcohol is a leading risk factor for the causes of death that are more prevalent among younger individuals: unintentional injuries and violence

[76]. It is hard to make inferences about the relationship between alcohol consumption and cognitive decline over time because study groups naturally age [17].

Residual confounding: Other healthy behaviors that coincide with moderate drinking may explain the observed decreased risk for cognitive decline among drinkers. Those who drink moderately tend to be better educated, have better diets, and smoke less. All of these are associated with a decreased risk of age-related cognitive impairment and dementia [77].

Glossary

- **Alcohol related brain damage (ARBD)** is a brain disorder that covers conditions including Wernicke-Korsakoff syndrome and is characterized by long-term decline in memory caused by long term excessive alcohol use.
- **Cardiometabolic diseases** include cardiovascular conditions, as well as metabolic dysfunctions such as diabetes and hypertension.
- **Cognitive decline** is the gradual erosion of healthy cognitive function.
- **Encephalopathy** is the broad term used to define damage or disease to the brain that alters brain function.
- **Episodic memory** is memory that can be recalled regarding one's personal past.
- **Executive function** is a collection of cognitive skills related to mental control and self-monitoring – inhibition, working memory, planning, and organizing – that allow an individual to perform everyday tasks.
- **Grey matter** is located on the surface of the brain and is made up of neuronal cell bodies present in every part of the brain and in the spinal cord.
- The **hippocampus** is the major brain structure associated with memory and learning processes.
- **Magnetic resonance imaging (MRI)** instruments can be used to take direct measurements of the brain structure.
- **Neurodegeneration** is the gradual loss of neurons or supporting cells that form the nervous system.
- **Neuron** and **nerve cells** are cells of the central nervous system that integrate and transmit information.
- **Neurotoxicity** refers to chemical, biological, or physical adverse effects to the nervous system from exposure to alcohol.
- **Verbal fluency**, also known as phonemic fluency, involves knowledge of letters and their relationship with word formation.
- **Visuospatial function** refers to the ability to identify and analyze spatial relations critical to movement, depth, and distance perception.
- **White matter** is found deep in the brain structure and provides insulation of nerve cells that improve electrical signaling.

Appendix

Table 1: cognitive domains and their respective brain region

Cognitive domains [78]	Brain region
Working memory/short term memory	frontal lobes [78, 79]
Executive function/problem solving	frontal lobe [78] and parietal lobes [79]
Attention	frontal lobes [78] and parietal lobes [80]
Verbal fluency/language/communication	parietal lobe [81]; frontal and temporal
Sensory and motor functions	sensory cortex/ motor cortex [82], cerebellum [83]
Verbal learning	temporal lobes [84]
Verbal memory	temporal, frontal and parietal lobes [85]
Inhibition/impulsivity	frontal lobes [78, 86]
Visuospatial abilities	frontal lobes [87], parietal lobes and occipital lobes [88]
Speed of processing	frontal lobes, paretial lobes and temporal lobes [80]
Visual learning	occipital and frontal lobes [89]
Visual memory	frontal, parietal and occipital lobes [90]

Heavy, sustained alcohol consumption can also have long-term effects on the different neurotransmitters that control signaling between nerve cells in the brain:

- *Endocannabinoid signaling* between nerves can be disrupted by prolonged exposure to ethanol; this disruption can perpetuate addiction [91, 92].
- *Serotonin neurotransmitters* are also disrupted by heavy and sustained alcohol consumption and are involved in continuing alcohol addiction [93].
- *Glutamate neurotransmitter* receptors are overstimulated by ethanol, which can change the shape of nerves over time [94] and damage them, with repeated, heavy ethanol exposure causing degeneration of the frontal lobes [35].
- Alcohol consumption initially increases production of the neurotransmitter dopamine [95] but heavy alcohol consumption may have *neurotoxic* outcomes with the gradual loss of neurons in the brain [42].

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