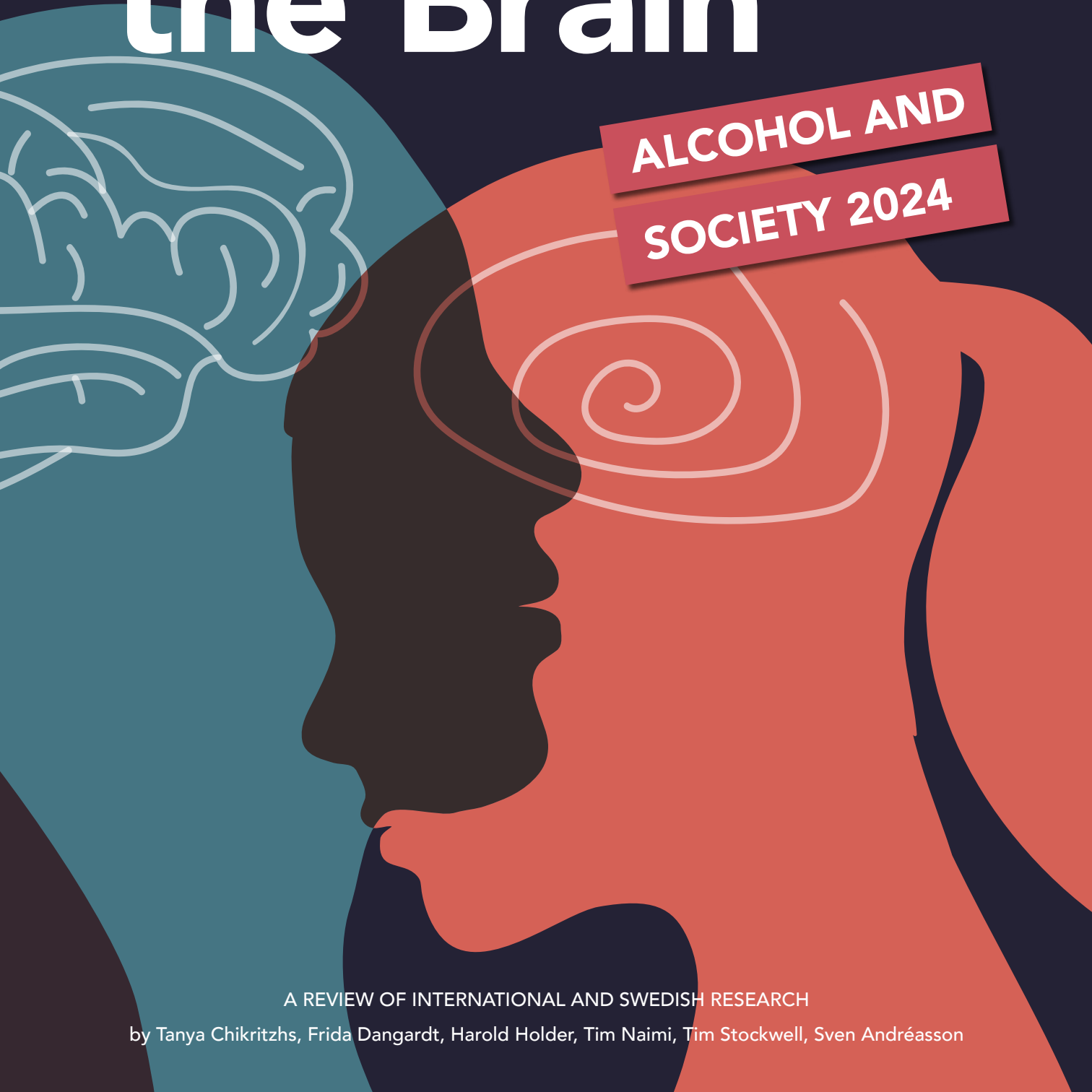
Alcohol and the Brain

ALCOHOL AND SOCIETY 2024



A REVIEW OF INTERNATIONAL AND SWEDISH RESEARCH

by Tanya Chikritzhs, Frida Dangardt, Harold Holder, Tim Naimi, Tim Stockwell, Sven Andréasson

Organisations initiating this report are voluntary or academic organisations independent of commercial interests.

CERA is an interdisciplinary and collaborative centre for education and research into hazardous use, abuse and addiction at Gothenburg University – which works to strengthen and develop research and education in the field of addiction, and to disseminate scientific expertise to people working professionally in the field of abuse and addiction, and other interested parties.

The Swedish Brain Foundation (Hjärnfonden) works for a society free of brain disease. The Swedish Brain Foundation raises money for research and information about the brain and its diseases, injuries and disabilities. and works to increase knowledge among the general public.

IOGT-NTO focuses on the effects of alcohol and narcotics on individuals and society, but is also engaged in broad social and club activities.

Junis is a child rights organization that offers environments and activities where children are free to be children. Junis runs local clubs across the whole of Sweden where the children have a say in planning the activities. We advocate for the right to a safe childhood free of alcohol and other drugs. Everything we do is based on principles of democracy, solidarity and soberness.

Movendi International is the largest independent global movement for development through alcohol prevention. Movendi unite, strengthen and empower civil society to address alcohol as serious obstacles to development on personal, community, societal and global level.

SFAM is the professional and scientific college of general practitioners (family physicians) in Sweden with continuing professional development, training of future GPs, assessment of competence, quality improvement and research in general practice/family medicine as main areas of interest.

The foundation **Stiftelsen Ansvar För Framtiden** aim to further Nordic cooperation and scientific research regarding sober life styles, public opinion in this regard, as well as care of children. The foundation have eight member organisations in three Nordic countries.

The **Swedish Society of Addiction Medicine** works to promote research and education in the addiction medicine field, and professional development in all specialist care professions.

The Swedish Society of Nursing is a nonprofit organization and a forum for discussing and developing nursing care by promoting nursing research, ethics, education and quality in nursing.

Sveriges Landsråd för Alkohol- och Narkotikafrågor is an umbrella organisation for county temperance organisations in Sweden and other organisations who work for restrictive alcohol and drug policies.

UNF is an NGO of young people for young people. UNF provides opportunities for youth to development, influence society and simply to spend time with awesome people. All activities, projects, programs and campaigns are created by young people, for young people.

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Foreword

This report, Alcohol and the Brain, is the tenth written by a group of international alcohol researchers initiated by many Nordic voluntary and academic organizations. Prior reports have covered several areas of importance to society that are affected by alcohol including youth, older people, violence, fetal effects, cancer and harm to others.

Each of these reports has followed a similar process. First, the expert research group selects one topic from several suggested by initiating organizations as having unique social relevance. Then, the group reviews extensively the published scientific research on that topic. By weighing evidence across different types of research designs, analyses, and settings, the group reaches conclusions based on best scientific evidence.

This report on alcohol and the brain reaches across earlier reports in the series. Many of the effects of alcohol relate to the brain including youth, violence, education, work-life, old age, and pregnancy. A great number of diseases are impacted by alcohol through its toxic effects on tissues and organs of the human body including the brain. Many pervasive social effects can be traced to physiological and psychological effects of alcohol on human behavior.

All reports have been written to inform the general public about the consequences of alcohol consumption and to inform policy makers about measures which can be taken to reduce harms from the sale of alcohol in society. Raising knowledge of these connections can help ensure that these relationships are understood and appreciated for their scope and magnitude. Given the many areas in society and human life touched by alcohol there are still many potential topics to explore. It is the research group's hope that this work will continue for many years still and that the reports find new readers and uses.

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Harold D. Holder
PhD Chair

Executive summary

- Ethanol, the active ingredient in alcoholic beverages, has widespread negative impacts on the human brain. Ethanol affects most structures within the brain, causes many types of short- and long-term brain impairments, and leads to a variety of neurological and non-neurological problems across all age groups.
- Alcohol (as ethanol) easily crosses the blood-brain barrier, reaching all structures in the brain. Alcohol is poisonous to brain cells.
- From youth through to old age, alcohol use can cause:
  - (i) acute or immediate impairment due to the presence of alcohol in the bloodstream which influences a range of behavioural/performance skills and increases risk of injury, e.g. road crashes, violence, falls;
  - (ii) longer-term cognitive deficits that emerge as cumulative effects presenting as decision-making difficulty among younger people, learning disabilities and poor educational performance, and forgetfulness or dementia among older drinkers;
  - (iii) emergence of alcohol dependence where increasing regularity and quantity of use sets in place processes that may progress towards difficulty controlling intake despite negative social or other consequences.
- Fetal alcohol exposure can cause permanent structural and functional brain changes and result in life-long learning, behavioural and health problems for the child. No safe level of alcohol use during pregnancy has been identified.
- Significant brain development continues throughout adolescence and young adulthood with key brain regions highly susceptible to adverse effects of alcohol, particularly "binge drinking" (drinking to the point of intoxication, with high blood alcohol concentrations [BACs]). High BACs increase impulsivity and the risk of injuries in violence; in the case of traumatic brain injury the damage is permanent and the effects lifelong. Binge drinking among adolescents is also a major risk factor for dementia later in life.
- Heavy drinking is an important risk factor for depression and suicide.
- For the ageing brain, alcohol use – particularly that above low levels – is a key risk factor for three neurological or neurologically-mediated conditions that are often lethal or otherwise disabling: dementia, stroke and falls. The more one drinks in life, the less brain matter exists later in life. Alcohol consumption can cause high blood pressure, which is the major risk factor for stroke. Alcohol can act independently or interact with a variety of medications that can lead to increased drowsiness, gait instability, and fall risk.
- Many of these conditions can be improved by reducing or stopping drinking. While some of the alcohol-related harms are irreversible e.g. FASD and some of the traumatic brain injuries it is important to recognize that much of the brain harms are reversible (e.g. alcohol dependence).
- Reducing alcohol consumption (both total consumption as well as binge drinking) is arguably the most important modifiable way to promote cognitive and neurological health and prevent or reduce brain harms.
- This can be achieved through effective alcohol control policies (e.g. policies to raise the price and reduce the availability of alcohol), health care screening and treatment resources including medications to treat alcohol dependence, and individual-level information and behaviour change informed by drinking guidelines.

Authors

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She has qualifications in epidemiology and biostatistics, some 20 years experience in alcohol research and a national profile as an expert in her field. Her research covers many areas of alcohol policy and alcohol epidemiology, such as alcohol consumption, alcohol related harms, alcohol taxation, liquor licensing, alcohol and heart disease, and alcohol and cancer.

She has received many awards including the prestigious Commonwealth Health Ministers Award for Excellence in Health and Medical Research and an NHMRC Achievement Award (1st ranked in Population Health).

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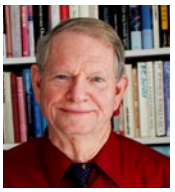

Harold Holder, Ph.D., is a Senior Research Scientist Emeritus and the former Director of the Prevention Research Center (PRC) of the Pacific Institute for Research and Evaluation, a national center for prevention research, located in Berkeley, California, USA.

Dr. Holder holds a doctorate in communication science and mathematical sociology from Syracuse University. He has explored two major alcohol research areas: the prevention of substance abuse, and the cost and benefits of alcoholism and drug abuse treatment and published work on the impact of changes in retail sales of wine and spirits on drinking and alcohol-involved traffic crashes. His policy studies also include assessments of the prevention potential of alcohol server liability, mandated server training, and environmental strategies as part of comprehensive approaches to prevention. Dr. Holder

has undertaken a series of collaborative studies in the Nordic Countries to study the effects of public policies. These collaborations with researchers from Sweden, Norway, and Finland concern the role and changes in alcohol policy resulting from membership or association in the European Union. In addition, Dr. Holder has participated with prevention scientists from a dozen countries in international projects to document the effects of alcohol policy. The projects have produced three books in which he was a co-author, Alcohol Policy and the Public Good (1994), Alcohol: no ordinary commodity – Research and public policy (2003) and Alcohol: no ordinary commodity, second edition (2010). His most recent professional work has entailed working with a number of U.S. states and local communities on the application of prevention science to practice.

Recently Dr. Holder chaired an international research group in an evaluation of Swedish research on alcohol, narcotics, doping, tobacco and gambling for the Swedish Council for Working Life and Social Research. The evaluation report was published in 2012.

Dr. Holder has received the 1995 Jellinek Memorial Award, awarded for distinction gained by advancing knowledge about alcoholism or fostering its study, treatment, or prevention.

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Tim Stockwell is scientist at, and was Director from 2004 to 2020 of, the Canadian Institute for Substance Use Research (formerly the Centre for Addictions Research of BC), University of Victoria, BC, Canada. He was previously Director of Australia's National Drug Research Institute and Director of Australia's Alcohol Education and Research Foundation. He is member of Canada's National Alcohol Strategy Advisory Committee and of WHO's Technical Advisory Groups on a) alcohol and drug epidemiology b) alcohol labelling.

Tim Stockwell holds degrees from Oxford University (MA Hons, Psychology and Philosophy), University of Surrey (MSc Clinical Psychology) and the University of London (PhD Institute of Psychiatry). His research has covered many aspects of substance use policy, prevention, treatment methods, liquor licensing issues, taxation and the measurement of drinking patterns and their consequences.

He is a Fellow of the Royal Society of Canada and past recipient of the 2013 international E.M. Jellinek Memorial Award for Outstanding Research on Alcohol Policy.

1 Introduction

In this report we focus on alcohol and the human brain. Our review draws together evidence for alcohol's broad ranging and often profoundly adverse impacts on neurological, cognitive and psychological health across the life course.

Reducing or eliminating alcohol consumption is arguably the most important modifiable way to promote cognitive and neurological health. Conversely, ethanol, the active ingredient in alcoholic beverages, has more negative impacts on the human brain than perhaps any other chemical originating outside the human body. This is because ethanol affects most structures within the brain and causes many types of short- and long-term brain impairments which lead to a variety of neurological problems across all age groups.

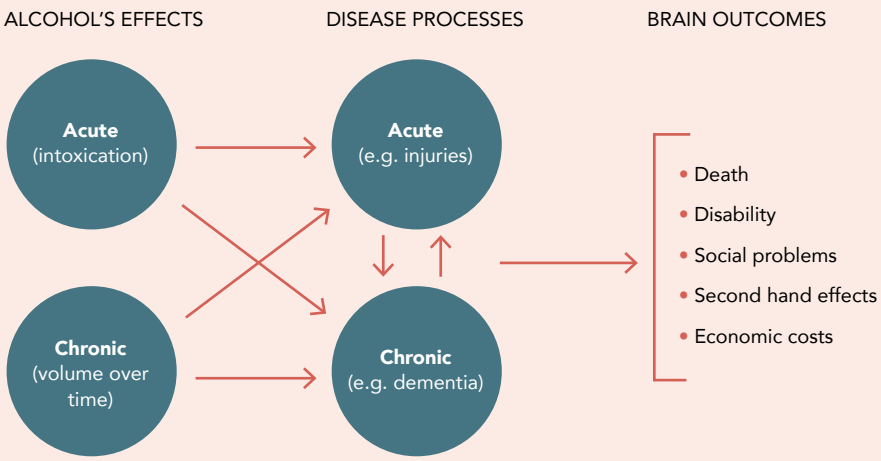
Alcohol and its primary metabolite acetaldehyde, are neurotoxins, which means that they are poisonous to neurons, the main type of brain cell. Alcohol easily passes from the bloodstream across the blood-brain-barrier, reaching all the structures in the brain including the cerebral cortex (involved in high-level thought), the cerebellum (balance and coordination), and the brainstem (responsible for breathing, wakefulness, etc.). Alcohol can also affect the part of the nervous system outside of the brain and spinal cord known as the peripheral nervous system. Alcohol-caused problems related to the peripheral nervous system include numbness in the hands and feet (i.e. neuropathy) and erectile dysfunction.

1.1 Multiple mechanisms

Alcohol affects the brain through multiple mechanisms. Some of them are acute, meaning that there is immediate impairment (i.e. brain dysfunction). Impairment refers to reduced ability to perform certain tasks and functions. Acute alcohol-related impairment has multiple dimensions in the form of altered mood (e.g. dysphoria, increased sociability) and decrements in judgment, impulse control, cognition and physical performance. Sometimes these acute effects can combine to cause problems. For example, alcohol-related car crashes are generally caused by the acute effects of alcohol. But what contributes to the event might include reduced executive functioning (e.g. impaired driver fails to notice it might not be a good idea to drive a car, or that it's a good idea to wear a seatbelt), loss of impulse control that could lead to faster driving speed, plus slower reaction time to apply the brakes or otherwise avoid crashing. Similarly, in the case of an alcohol-caused drowning, impaired swimming performance might be accompanied by loss of executive functioning and misjudgement of swimming conditions or one's swimming ability. A number of conditions caused by acute alcohol consumption can lead to chronic brain problems. An example of this would be an acquired traumatic brain injury, where acute impairment leads to an injury to the brain or spinal cord resulting in lifelong neurological and or cognitive disability.

Ethanol, the active ingredient in alcoholic beverages, has more negative impacts on the human brain than perhaps any other chemical originating outside the human body.

ALCOHOL EFFECTS, DISEASE PROCESSES AND BRAIN OUTCOMES



Acute and chronic alcohol consumption increase risks of both acute and chronic diseases, which can interact, and lead to brain-related outcomes.

Alcohol also has chronic effects on the brain, meaning that it can cause lasting damage.[1,2] Most damage is caused by heavy consumption over a long period of time (typically years or decades). However, high levels of consumption for shorter time periods that result in very high blood alcohol concentrations can also cause lasting damage and subsequent cognitive difficulties. Alcohol consumption can over time lead to chronic structural changes in the CNS including generalized cortical and cerebellar atrophy.[3] Studies using Magnetic Resonance Imageing (MRI) to measure changes from alcohol consumption in the brain typically find loss of brain volume, with greater loss at higher levels of consumption. Studies also show that the brain in older age may be more vulnerable to the effects of alcohol. Research using MRI is important in order to increase our understanding of effects of alcohol on the brain, but strucutral brain changes alone are not sufficient to make conclusions of harm.[4]

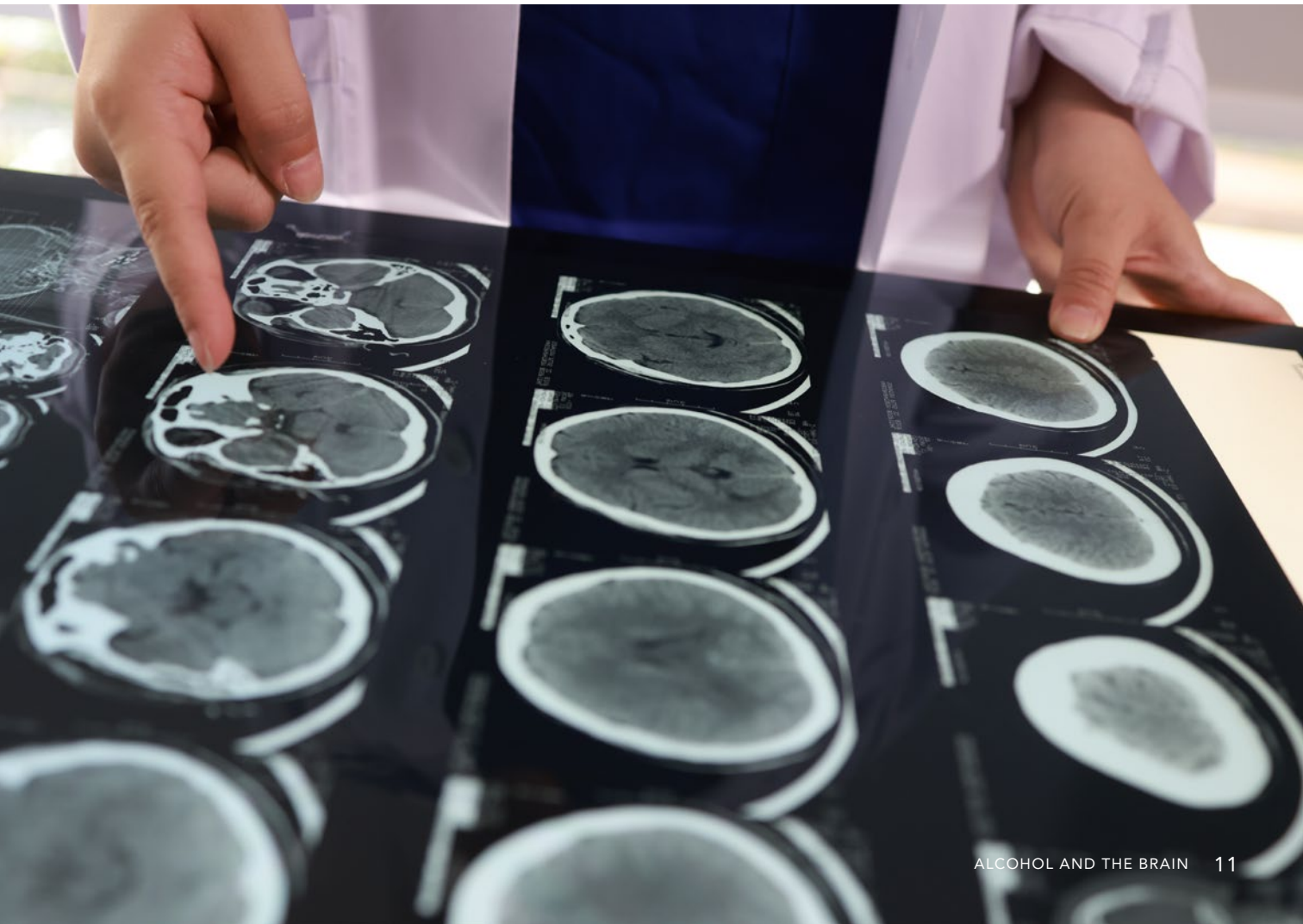
Chronic effects can lead to chronic medical conditions such as dementia or alcohol use disorder (i.e. alcohol addiction). Chronic alcohol consumption can also increase the risk of acute conditions that then lead to chronic deficits; an example of this would be haemorrhagic stroke, which can, after years of regular drinking, occur suddenly and result in lingering deficits. Acute and chronic effects of alcohol can also combine to cause health problems. For example, suicide commonly occurs in the setting of depression, and heavy alcohol use can either cause or exacerbate depression. But acute impairment from alcohol can also lessen impulse control that might otherwise protect a depressed person from trying to harm him or herself.

1.2 Effects across the life course

As noted above, alcohol contributes to a variety of neurological problems across all age groups. Alcohol is the leading preventable cause of mental disability worldwide. Fetal

alcohol syndrome (FAS), caused by exposure to ethanol in utero, causes developmental delay, intellectual disability, stunted physical growth, and characteristic facial features. Beyond FAS, there is also fetal alcohol spectrum disorder (FASD). Though generally less severe than FAS, FASD is far more prevalent in the population and may be associated with important, common childhood conditions such as learning disabilities and attention deficit hyperactivity disorder.

In children and young adults, much of the impact of alcohol relates to acute impairment, with attendant medical and social problems. Chief among these are unintentional injuries (e.g. traffic crashes, poisonings) and interpersonal violence, including sexual violence. The relationship between alcohol and injuries has been well established and is mediated through the acute effects of alcohol discussed earlier. Degree of impairment is closely related to blood alcohol concentration (BAC), which is determined by the number of drinks consumed in a given time period, modified by body mass, sex and other factors. For motor vehicle crashes, risk of injury at any BAC is greater for younger or less experienced drivers compared with older adults. Poisonings, including fatal overdoses, are also neurological events because they involve respiratory depression/cessation, and alcohol is a respiratory depressant at high BACs. A substantial fraction of opioid overdose fatalities also involve alcohol, which may be a contributing or predominant factor in these deaths. In terms of violence, lethal outcomes include suicide and homicide. Alcohol is a prevalent risk factor for both of



Among adult populations generally, chronic heavy alcohol use can play a causal or contributing role in the onset of depression, which is a major cause of disability and social problems and a risk factor for suicide

these conditions, mediated though it's acute impacts on mood and impulsivity. In addition to death, injuries can result in lifelong disability (e.g. traumatic brain injury, other permanent physical injuries). Heavy drinking (high total amounts) and binge drinking (high per-occasion amounts, typically defined as drinking 4 or more drinks) can also change the architecture and function of the adolescent and young adult brain, and thus contribute to cognitive problems relatively early in the life course that may become more pronounced in later life.[1,2] (See Section 3 for more detailed discussion of alcohol's effect on the developing brain).

Among adult populations generally, chronic heavy alcohol use can play a causal or contributing role in the onset of depression, which is a major cause of disability and social problems and a risk factor for suicide (see Section 4). At low levels of consumption some may find alcohol to be relaxing, but at higher levels of consumption alcohol can contribute to anxiety and exacerbate anxiety disorder. Alcohol use disorder, commonly referred to as alcohol dependence, can also be regarded as an important alcohol-caused neurological condition. For those who drink heavily, alcohol withdrawal syndrome can be a life-threatening neurological condition that consists of hallucinations, delirium, tremors and sometimes withdrawal seizures. Alcohol can also contribute to other seizure disorders through a range of direct and indirect effects such as lowering the "threshold" for a seizure event, decreasing medication adherence and, causing seizures from acquired alcohol-caused traumatic brain injury. Other common but less lethal neurological problems that can be exacerbated by alcohol include headaches and sleep disturbances. For migraine headaches, alcohol is a common trigger[5], whereas heavy drinking and hangovers are associated with tension-type headaches. Even though alcohol consumption may help some people fall asleep initially, alcohol even in low doses disrupts sleep architecture, both in adults and adolescents, and commonly contributes to sleep disturbances and sleep disorders.[6-8]

For older adults, dementia and stroke are extremely important conditions related to alcohol consumption; the relation between alcohol and dementia is covered in Section 5. Alcohol consumption is the sole cause of alcoholic dementia, which is characterized by cerebral atrophy and deficits in multiple areas of cognition.[9] Alcohol is associated with a greater risk of multiple forms of dementia,

BOX 1 TYPES OF SCIENTIFIC EVIDENCE

Types of scientific studies considered in this report are of following types:

Mendelian randomization studies are those that rely on genetic variants that are related to alcohol consumption in order to indirectly study effects of alcohol consumption.

Randomized controlled trials "flip a coin" to randomly assign one group of participants to an intervention and another to not partaking of that intervention (e.g. experimental lab studies that administer alcohol to participants in the intervention group).

Observational studies generally use data obtained from non-randomly "observing" participant self-reports of alcohol use to investigate whether drinking affects risk of mortality or morbidity from various diseases.

Neuroimaging studies use non-invasive imaging technology (e.g. Magnetic Resonance Imagining [MRI]) to study the structure and function of the brain and central nervous system under certain conditions (e.g. presence or absence of alcohol).

Each type of study brings its own strengths and weaknesses. As discussed in previous reports and explained here in Box 2, non-randomized observational studies are particularly prone to finding spurious protective effects from low-to-moderate alcohol intake for conditions that are more likely to occur in middle and older age.

including Alzheimer's disease, especially at higher consumption levels. There is a positive, linear association between how much alcohol consumed during one's lifetime and the amount of cerebral atrophy (i.e. brain wasting) seen on brain scans (e.g. CT, MRI). Alcohol consumption is a risk factor for haemorrhagic stroke (the type of stroke when a blood vessel in the brain bursts) and ischemic stroke (the type of stroke where a blood vessel is blocked). One of the main mechanisms for this is that alcohol consumption above two drinks a day can raise blood pressure, and high blood pressure is a major stroke risk factor. Binge drinking is a strong risk factor for both haemorrhagic and ischemic stroke.[10] Alcohol can increase the risk of falls through acute and chronic effects on balance, strength and sensation in the feet and legs, all of which can contribute to unsteadiness, which increase the risk of falls. Alcohol can also interact with a variety of medications that can lead to increased drowsiness, gait instability, and fall risk.[11] Patients with greater cerebral atrophy due to alcohol or another cause are also at increased risk of intracranial bleeding due to falls than those without atrophy.

1.3 Summary of contents and methods used in this report

The remainder of this report will explore alcohol's short- and long-term effects on: brain function, structure and potential mechanisms underlying harms (section 2); the developing brain (section 3), mental health from youth through middle-age (section 4); and the ageing brain (section 5). Section 6 provides recommendations and outlines policy interventions that can reduce alcohol's harms. Although the subject of alcohol in the brain is broad and also complex, reduced consumption in the population is critical to preventing and reducing alcohol-caused brain problems. Although public awareness of alcohol-brain relationships are important, and treatment is critical for those with an alcohol use disorder, implementation of effective alcohol control policies can yield the population-based changes in alcohol consumption required to meaningfully reduce alcohol's contributions to neurological, cognitive and psychiatric problems attributable to alcohol.

In preparing this report, we have reviewed a wide range of relevant literature with a particular focus on comprehensive and systematic reviews, on studies providing examples from Sweden and the Nordic countries and on studies with more rigorous designs. In Box 1 we summarise some major types of research design referred to frequently in this report. Randomised controlled and Mendelian randomisation studies will be given more weight than uncontrolled, observational studies. Systematic reviews were given special priority, particularly where they identify higher quality and more rigorous studies. Such reviews ensure a comprehensive search of all published relevant studies, usually followed by the selection of those meeting criteria for being of higher quality.

Although the subject of alcohol in the brain is broad and also complex, reduced consumption in the population is critical to preventing and reducing alcohol-caused brain problems.

There are various reasons why apparent protective effects from low-to-moderate alcohol use are unlikely to reflect genuine health benefits.

BOX 2 APPARENT BUT IMPLAUSIBLE HEALTH BENEFITS OF LOW-TO-MODERATE ALCOHOL USE

Throughout this report, the issue of apparent health benefits (i.e. protective effects) from drinking at low-to-moderate levels (compared to not drinking) occurs under almost every topic considered. This recurring theme of apparent protection, which we have drawn attention to in previous reports, highlights the difficulty inherent to interpreting results from (non-random) observational studies which aim to investigate associations between complex and changeable alcohol use behaviours and health.

There are various reasons why apparent protective effects from low-to-moderate alcohol use are unlikely to reflect genuine health benefits. In the first place, the ubiquity of this finding across diverse and unrelated conditions within the observational study literature points to unresolved methodological weaknesses being a more likely explanation. Alcohol use has for instance been reported (implausibly) to reduce risk of deafness, common cold, some cancers, liver cirrhosis and even to benefit children exposed to alcohol during pregnancy.[12] Examples of apparent protective effects from low-to-moderate alcohol use described in this report include: (i) improved cognitive and emotional development of infants whose mothers drank alcohol during pregnancy; (ii) superior educational attainment among young adults; (iii) improved cognitive abilities of adolescents and adults; (iv) better mental health and less depression among adults; and, (v) reduced risk of dementia among older people.

Methodological critiques have pointed to three key problems pervasive in the observational research literature on alcohol: residual confounding, misclassification error and reverse causation. (i) In addition to their alcohol use, low-to-moderate drinkers are also characteristically different from their non-drinker counterparts in ways other that can protect against illness and injury e.g. higher income, better diet, more exercise, better access to healthcare.[13] When these other differences are not fully accounted for, residual confounding can make it appear as if the low-to-moderate drinker group is in better health due to their alcohol use. (ii) Misclassification error occurs when study drinking groups (e.g. non-drinkers, low level drinkers, heavy drinkers) do not accurately reflect actual alcohol exposure of participants in those groups. This is highly problematic when the non-drinker group (presumed to be unexposed to alcohol), against which drinkers are usually compared, in fact contains many people who once drank alcohol (often heavily). Most people change their drinking status as they age and many who were heavy drinkers in their 20s and 30s become ex-drinkers in their middle years due to increased ill-health and frailty. Because change in alcohol use over time is not independent of health, misclassification error is a serious problem for studies that recruit middle-aged and older people and then fail to classify participants on the basis of their true lifetime exposure.[14-16] (iii) The phenomenon of "reverse causation" may underpin many unexpected findings that arise from observational studies.[17,18] Observational studies are not well suited to determining cause and effect, especially when behaviors change over time. In reverse causality, what is presumed (incorrectly), by the research study to be the "effect" (e.g. the disease) actually precedes what is presumed (incorrectly), to be the "cause" (e.g. alcohol use or absence of alcohol use). For example, people who become depressed may reduce participation in activities which, for many, involve drinking (e.g. attending dinner parties, socializing at sports clubs) or simply lose interest in alcohol use per se. A study which suffers from reverse causation will measure alcohol use and depression and erroneously conclude that absence of alcohol use leads to depression.

Taking all these factors into account, we take a sceptical view of reported benefits of low-to-moderate drinking unless they are supported by randomised controlled or Mendelian randomisation studies (which are less susceptible to reverse causation and residual confounding than observational studies). Where applicable, this issue will be noted again throughout each section of the report.

Summary

Is low-to-moderate drinking a panacea for all ills?

Published studies (implausibly) suggest low-to-moderate drinking protects against a diverse range of unrelated health problems (e.g. deafness, the common cold, liver cirrhosis, cancer, educational attainment, cognitive functioning and mental health across the life-course). These apparent benefits are implausible because:

- Low-to-moderate drinkers have many health protective behaviours and characteristics unrelated to their drinking e.g. higher income, better diet and access to healthcare.
- Low-to-moderate drinkers are usually compared with abstainers who may have stopped or cut down on drinking because of poor health.
- Observational studies of alcohol and disease are prone to reverse causation.

2 Ways in which alcohol use can impair brain function and behaviour

In this section we discuss and present evidence for ways in which alcohol use can impact brain functioning and behaviours in both the short and longer term as well as performance level when completing complex tasks as a part of normal life. We will consider three key processes:

(i) Acute impairment

Acute impairments are short-term effects that occur when alcohol is present in the bloodstream. Alcohol reaches the brain about 5 minutes after drinking and begins to affect cognitive functioning and behaviour within about 10 minutes. Acute impairment of cognitive abilities and motor skill performance when completing complex tasks may last a few hours at most depending on the dose.

(ii) Longer-term and cumulative cognitive deficits

We also focus on longer-term impacts that endure for days, weeks or even years after drinking, or occur as cumulative effects from using alcohol regularly over time. As longer-term harms accumulate over the life course they can be harder to reverse as people approach older age. Pre-natal alcohol exposure presents special risks and may cause irreversible structural changes to the developing brain.

Alcohol use, especially at higher levels, can disrupt such smooth functioning, thus exposing drinkers and those around them to different kinds of injury risks.

(iii) Alcohol dependence

As people use alcohol with increasing regularity and in larger amounts, physiological and psychological changes that lead to difficulties controlling intake to moderate levels may occur. Increased craving for alcohol in a range of regularly encountered situations can ensue and even when negative social or other consequences arise, resisting drinking can be very difficult.

We will discuss evidence for each of these key processes that may result in drinkers experiencing serious harms, as well as areas of the brain that may be critically involved. In each case we will consider effects of dose of alcohol and the extent to which these processes and associated harms may be reversed as people age.

2.1 Acute impairment

Acute impairment resulting from drinking can have implications for undertaking complicated tasks as a part of routine life in the moment. In this section we discuss research concerning impacts of alcohol on overall performance, with specific examples from the scientific literature on driving and aggression/violence, as well as short- and long-term cognitive functioning.

Performance decay and brain function

As a part of our daily lives, we humans must complete or carry out many complex tasks such as cooking, looking after children, completing work-related tasks (e.g. operating complex machinery), driving motor vehicles, socializing, resolving conflicts and undertaking home maintenance. These tasks, while commonplace, each require high levels of information processing, decision-making and motor skills which depend on smooth functioning of the brain and central nervous systems (CNS). Alcohol use, especially at higher levels, can disrupt such smooth functioning, thus exposing drinkers and those around them to different kinds of injury risks.

Potential effects of alcohol-induced brain impairment on performance of complex tasks have been discussed in our earlier reports (e.g. [11,19-21]). The topic of alcohol-impaired driving for instance, has been extensively studied and alcohol is accepted as a major risk factor for road crashes by laypeople and scientists alike. Landmark reviews and meta-analyses of observational studies (e.g. [22,23]); have, for many years, provided convincing evidence for the causal role that alcohol plays in both fatal and non-fatal road injuries, as well as other non-crash related injuries (e.g. falls, violence). Findings from these observational studies are consistently confirmed by experimental laboratory and driving simulation studies (e.g. [24]).

Many randomized experimental studies have examined alcohol's impacts on a range of behavioural/performance skills required for safe driving, occupational activities e.g. operating machinery or industrial manufacturing equipment, other every-day tasks and generally avoiding injury.[25] What's more, the degree of impairment is strongly related to the amount of alcohol consumed (i.e. a dose-response relationship), that is, as BAC increases, performance declines and risk of injury increases.[23] A careful experimental study by Dawson & Reid (1997)[26] for example, had 40 people perform unpredictable hand–eye coordination (tracking) tasks while drinking about one alcoholic drink every 30 minutes and until their blood alcohol reached 0.10%. For each 0.01% increase in BAC, cognitive performance decreased by 1.16% i.e. at a BAC of 0.10%, performance decreased, on average, by 11.6%.

Experimental lab and neuroimaging studies (e.g. MRI) concur that alcohol impairs specific brain centres and CNS processes. Extensive reviews, some of over 200 experimental studies (e.g. [27]) conducted on alcohol's acute effects on the brain and CNS have confirmed impairments for visuo-motor control (i.e. eye-hand-foot coordination), divided and focused attention, reaction time, response inhibition and threat detection, motivation and reward-seeking, spatial learning and working memory.[25] These

findings are consistently supported by high resolution neuroimaging studies that detect alcohol-induced changes in brain metabolism (i.e. shift from glucose to acetate metabolism) and structure, even at low doses. These changes are centred in brain regions thought to be critical to behavioural/performance skills including the cerebellum, hippocampus, occipital cortex, striatum and amygdala (e.g. [28,29]).

Alcohol-impaired driving studies

From a global perspective, the proportion of crash fatalities caused by alcohol-impaired drivers varies by region. This variability occurs largely as a function of alcohol availability and drink-driving law enforcement rather than country-to-country differences in how alcohol affects the human brain.[25] WHO regional estimates for broad regions suggest that prevalence ranges from about 2% in the Eastern Mediterranean where alcohol consumption is largely prohibited, to almost 38% in Europe where alcohol is widely available.[30] For non-fatal injuries there is also large between-country variability and prevalence ranges from 5.5% in the Middle East, North Africa, and Greater Arabia region to about 30% in the Asia region and 46% in the WHO-South Africa region.[31,32] A recent review of 60 observational studies[33] confirmed earlier meta-analyses (e.g. [23]) that showed the relationship between BAC and crash injury risk to be exponential. Interestingly, they also found the relationship was strongest among studies from Nordic countries and they suggested, "This may be due to a higher prevalence of aberrant behaviors and health problems among drunk drivers in Nordic countries,

Even at very lows BAC (e.g. 0.015%), a driver's ability to divide attention between two or more sources of visual information may be impaired.

where drunk driving is less common than in other countries."[33]

The effect of BAC level differs across different types of performance skill and the World Health Organization[34] reports evidence that alcohol impairs attention, perception, and vigilance at different BAC levels. A comprehensive review by Moskowitz (2000)[35] found that impairment of driving skills began with any increase above zero BAC, that most studies found impairment at BACs of 0.05% and nearly all (94%) did so at 0.08% or above. Rezaee-Zavareh et al. (2017)[36] reviewed 13 randomized trials of simulated driving performance comparing drivers given alcohol and those not. Nearly all performance measures deteriorated significantly with alcohol administration. Similarly, Irwin et al (2017)[24] reviewed 37 trials with a total of 721 participants where a "placebo alcohol" control was used versus real alcohol administration, confirming that performance decrements with alcohol were not simply due to expectancy effects. A review by Martin et al. (2013)[22] focused on low-to-moderate BAC effects (≤ 0.1%) and reported that BAC level and task complexity were more profound factors in performance levels than were age, gender, driving skill, and alcohol tolerance. Even at very lows BAC (e.g. 0.015%), a driver's ability to divide attention between two or more sources of visual information may be impaired.[37] Several reviews and individual studies have concluded there are no thresholds of BAC below which there is no impairment. It is noteworthy that in Sweden and Norway legal limits for blood alcohol while driving are currently among the lowest in the world (i.e. 0.02%).[38]

Studies on alcohol and aggression

Many experimental studies have examined whether alcohol, necessarily at relatively low doses (two to four drinks), can impair control

of aggressive behaviours as simulated in some laboratory tasks (e.g. administering fictitious "electric shocks" to a fellow participant for poor performance). These placebo-controlled designs test whether increased observed effects are due to a pharmacological or "expectancy" effects.

Several pathways by which alcohol use may cause aggression have been proposed. Exum (2006)[39] theorized that alcohol can suppress inhibition of innate aggressive responses, based upon biological evidence that alcohol use impairs higher level brain functions including working memory, planning and response inhibition. Intoxicated individuals tend to focus on more immediate situational cues than future consequences.[40] They also have more difficulty interpreting facial and vocal expressions and have reduced empathy.[41] Even within the low alcohol doses used in these experiments, dose-response effects have been demonstrated suggesting aggressive behaviour is even more likely at higher BACs.[39] This same review also concluded that expectancy effects i.e. the belief alone that alcohol had been consumed, had minimal or no effects on aggression.

Studies looking at possible effects on sexual aggression support the view that alcohol's pharmacological effects are real and are associated with misperceptions of sexual arousal, sexual cues and willingness of the victim.[40,42] Interestingly, women given placebos also anticipated that they would be more likely to engage in risky behaviours when drinking, suggesting expectancy as well as pharmacological effects.

A third theoretical mechanism is that the pharmacological effects of alcohol cause additional cognitive, emotional and physiological changes[43] that predispose towards aggressive behaviours. Drinkers may, for example, be more susceptible to provocation and frustration. Most reviews of laboratory studies conclude that the pharmacological effects of alcohol are indeed an important contributing cause of aggression under some specific circumstances.[39-41] A causal relationship between alcohol's pharmacological effects and aggression is also supported by findings from animal studies.[41]

2.2 Longer term cognitive deficits

Even a single exposure to a high blood alcohol can lead to measurable impairment of cognitive abilities several weeks later. Negative impacts on cognitive ability are related directly to the number of blood alcohol exposure episodes, their severity and duration. With repetition, these impacts can accumulate over time. Meanwhile, the extent of recovery possible from these impacts decreases with advancing age. At the other extreme, if alcohol exposure occurs before birth when the brain is at its most vulnerable, the resultant injuries can also be profound and lifelong. Adolescence is also a period in which the brain is still developing, when alcohol consumption often starts and when its use may lead to changes in brain structure and lasting cognitive deficits. Also, heavy episodic drinking in adolescents and young adulthood is a leading risk factor for early onset dementia.[44]

Several physiological mechanisms that can lead to cognitive impairment have been identified. Alcohol (as ethanol) readily crosses over the blood brain barrier where it is toxic to brain cells (i.e. alcohol is a neurotoxin) potentially resulting in short- and long-term tissue damage. Long-term heavy alcohol use can also lead to acute thiamine deficiency with profound potential impacts on learning and memory abilities e.g. Wernicke's encephalopathy and Korsakoff Syndrome.[4]

Types of cognitive deficits due to alcohol across the lifespan

Dannenhoffer et al (2021)[1] provide a comprehensive review of the kinds of cognitive deficits alcohol use may cause across different phases of the life course and the extent to which these can be reversed variously through avoiding alcohol or other treatments e.g. nutritional supplements. They conclude that "cognitive flexibility" as indicated by the

Intoxicated individuals tend to focus on more immediate situational cues than future consequences.

Pre-natal exposure to alcohol presents special risks to brain development at this most vulnerable of developmental stages. With exposure to high blood alcohol levels in utero, many children fail to develop important brain structures and may have smaller brain volumes overall.

ability to change behaviours in response to different cues is impacted by alcohol exposure at every stage of life. Further, although the ability to recover cognitive flexibility (learn new habits, unlearn old) can be substantial at young ages it increasingly deteriorates with advancing age. Deficits caused by alcohol exposure at a young age may persist to older ages and even the fully developed brain in young and middle-aged adults may be harmed by further exposures to a degree related to level and frequency of exposures. However, larger doses are required for adults to be measurably harmed by alcohol exposure than is the case for adolescents.

Pre-natal exposure to alcohol presents special risks to brain development at this most vulnerable of developmental stages. With exposure to high blood alcohol levels in utero, many children fail to develop important brain structures and may have smaller brain volumes overall.[45,46] Temporal lobes, which are associated with formation of memories, auditory processing, and language comprehension, are particularly affected. Damage to other brain structures can lead to poor motor control, learning disabilities, and behavioural inhibition. Typical brain development is associated with a large increase in cortical grey matter during early childhood followed by loss of cortical grey matter during late childhood and adolescence by condensing the synapses. Children diagnosed with fetal alcohol spectrum disorders (FASD) show region-specific loss of grey matter and decreased plasticity from early childhood through adolescence. One frequently observed effect is the disruption of brain plasticity. Animal models and human studies have demonstrated enduring deficits in learning and memory as well as abnormal plasticity in regions of the brain associated with these functions.[47]

Seemiller and Gould (2020)[48] reviewed evidence for alcohol's impact on cognitive functioning in adolescence, examining both human and animal studies. They concluded that harm is particularly evident in the prefrontal cortex area of the brain associated with new learning, judgement and behavioural control. Furthermore, repeated alcohol exposure during adolescence is associated with measurable impacts on cognitive function in later adult life.

Hua et al (2020)[49] reported evidence of measurable effects on brain functioning from a single heavy alcohol use occasion (in this case 21st birthday celebrations) with measurable structural changes in the brain and five week follow-up. Heavy drinking occasions seem to be particular risk factors among young adults for impacts on cognitive ability. Linden-Carmichael et al (2023)[50] found evidence for uniquely hazardous effects of "blackout drinking" i.e. drinking so much that there are memory blanks the next day. Measures of every-day forgetfulness and difficulties in decision-making were found to be significantly associated with the frequency of blackout drinking among young adults.

Association between alcohol use and cognitive ability

One method to assess the significance of alcohol exposure on brain function is to explore associations between alcohol use patterns and educational attainment among adolescents and young adults. In Sweden, recent reports indicate that the majority (57%) of adolescents don't drink alcohol. However, young people that do drink appear to have worse health and educational performance than their non-drinking peers.[51] In keeping with this, a systematic review found that 13 out of 16 studies reported significant negative associations between frequency of heavy episodic drinking (i.e. binge drinking) among adolescents and academic performance (i.e. heavy alcohol use associated with lower academic performance).[52]

Comprehensive tests of cognitive performance have also been conducted on large cohorts of people as they age while looking for associations with their current and past drinking. Garduno et al (2023)[53] for instance, found faster cognitive decline across multiple

cognitive tests among at-risk drinkers aged 57 years and older. What's more there was no convincing evidence for protective effects for low-to-moderate drinking. One complication of this literature is that many observational studies also tend to find that compared to abstinence, low-to-moderate, and sometimes heavy levels of alcohol consumption, are positively associated with higher socio-economic status (SES), educational attainment and income. This applies to younger adults as well as the whole population. A Norwegian cohort study of educational outcomes among young people aged 13 to 32 years is a notable example. The study's results suggest that while drunkenness in early teenage years was a marker of risk for poorer educational outcomes later in life, after 20 years of age, more frequent episodes of drunkenness predicted more favourable outcomes.[54] They also found that drunkenness in young adulthood was consistently associated with higher income and lower risk of disability. Taken together, findings suggest that design problems common to observational studies including residual confounding from socio-economic and health-related characteristics (e.g. higher income, better health) and reverse causation are at play here. Indeed, a large UK study that used a robust Mendelian randomization design – which is far less susceptible to reverse causation – showed that educational attainment predicts greater alcohol use rather than the other way around.[55]

Potential positive effects of alcohol consumption at different levels on cognitive function were also investigated in a recent Cochrane Review Australia report.[56] Their meta-analyses indicated that for women, consuming up to 26g of pure alcohol per day improved performance on cognitive function tests compared to no alcohol but

Heavy drinking among adolescents, mostly in the form of binge drinking, is a major risk factor for later development of dependence.

that performance deteriorated rapidly at higher doses. Men exhibited a similar pattern of effect with improvement peaking at 19g per day, i.e. 1.5 Swedish standard drinks per day. Unfortunately, the study used "current non-drinkers" as the comparison group and did not, or were unable to, exclude or apply an intention-to-treat approach to former drinkers. It has been well documented that former drinkers include many people who either can't drink or choose to stop doing so for health reasons. Thus, they are an imperfect control that biases results in a positive direction for current drinkers.

(For a more detailed discussion of misclassification error, residual confounding and reverse causation in observational studies see Box 2, page 14).

2.3 Alcohol dependence

With increasing alcohol consumption, the risk of dependence increases. What was originally a rewarding behaviour gets out of control. The primary symptoms of dependence are a strong or overwhelming desire for alcohol (craving) and impaired control over consumption (inability to stop drinking once begun). Both are a consequence of heavy drinking over time. In addition, craving leads to a prioritization of drinking, with increasing neglect of other interests and responsibilities. Heavy drinking also leads to physiological changes: tolerance increases, requiring larger amounts of alcohol to achieve the desired effect and withdrawal leads to unpleasant and potentially dangerous symptoms when drinking is discontinued. Often dissatisfaction with consumption is present, but attempts to reduce consumption fail. The core of dependence involves a drinker wishing to reduce or stop drinking, but is unable to do so – he or she is hooked.

Alcohol dependence is a function of high levels of consumption. Consequently, alcohol dependence is most prevalent among young adults, with gradually reduced prevalence over the life course. Heavy drinking among adolescents, mostly in the form of binge drinking, is a major risk factor for later development of dependence. In a national study in the US of 43 000 randomly selected people, 15% had developed alcohol dependence before the age of 18, 47% before the age of 21 and two thirds before the age of 25.[57] Thus, alcohol dependence is first and foremost a problem for young people.

Alcohol consumption activates the reward circuitry in the brain, which for some people leads to a release of dopamine, which is perceived as pleasurable. The majority of drinkers will not experience this effect however, as for them, drinking is largely motivated by other factors, mostly related to social/cultural norms. Drinking also affects the frontal cortex, with impairments in executive functions: judgement, planning, impulse control. Acutely, this occurs at rapid increases in blood alcohol content, which typically occurs during binge drinking. This is a major cause of the acute negative effects of drinking: accidents and violence. Long-term effects of impaired executive function contributes to difficulties in changing behaviour – in addition to a host of problems related to impaired cognitive function.

Alcohol dependence is defined in several ways. For many years the dominant view was that dependence was a chronic brain disease, with permanent damage to different parts of the brain. These impairments could be visualised with modern imaging techniques and have been interpreted as chronic damage. This view has been increasingly challenged. Epidemiological studies have found that the large majority of people that develop dependence come out of this condition after a number of years, mostly without receiving treatment. This would not be possible if there actually was permanent damage. But for a minority dependence persists, usually as a consequence of more severe forms of dependence. A major alternative description of dependence is that it is a problem of learned behaviour. The behavioural view accepts that alcohol and drugs affect different parts of the brain, making change difficult. But in

contrast to the chronicity view, the plasticity of the brain is emphasized. The brain has the capacity to change, and over time most people do change addictive behaviour, mostly without treatment.[58] Other views of addiction include impairment of the motivational system.[59] Some see it as rational choice, where people consciously choose to drink in spite of negative consequences. Others again see it as a visceral condition similar to hunger, thirst or pain. Genetics is seen as a strong determinant, where inheritance of drinking problems have been recognised since antiquity. Whether this inheritance is due to genetic factors or environmental factors is still a matter of controversy. Many see addiction as self-medication of psychological distress. A major controversy is whether dependence is a disease or not. An increasingly common view is that it should be regarded as a disease, but not necessarily as a chronic disease.

Summary

Alcohol (as ethanol) affects most structures within the brain causing many types of short- and long-term brain impairments. From youth through to old age, alcohol use can cause: (i) acute or immediate impairment due to the presence of alcohol in the bloodstream which influences a range of behavioural/ performance skills and increases risk of injury, e.g. road crashes, violence, falls; (ii) longer-term cognitive deficits that emerge as cumulative effects presenting as decision-making difficulty among younger people, learning disabilities and poor educational performance, and forgetfulness or dementia among older drinkers; (iii) emergence of alcohol dependence where increasing regularity and quantity of use sets in place processes that may progress towards difficulty controlling intake despite negative social or other consequences.

3 The developing brain – from fetus to young adult

3.1 Alcohol exposure before birth

Alcohol passes easily from a pregnant woman to her developing baby, potentially causing harm to the baby's growth and development. Alcohol exposure during pregnancy can have a profound impact on brain development in the fetus. This manifests as a range of symptoms in the baby and child and causes potential problems throughout the life course. Alcohol exposure during pregnancy is the most common cause of preventable intellectual disability in the world, estimated to affect 1–5% of live births each year.[46]

There are many possible biological pathways by which alcohol can harm the fetus, and the impact may differ depending on gestational stage. There are directly harmful effects during the embryonic and fetal stages of development, as well as toxic effects on the placenta, altered genetic expression and protein synthesis, hormonal alterations, and effects on the vascular development of both the placenta (causing hypoxia and growth retardation) and the fetus. Alcohol and its metabolite acetaldehyde also cause brain cell death, which, depending on the developmental stage, can cause a range of problems including central and peripheral nervous system and brain-derived hormonal regulation disruption. Other potential mechanisms include stem cell impairment, damage to sperm and egg DNA, disruption of genes responsible for regulating stress responses and genes responsible for blood vessel development in the brain and placenta (which can affect oxygen and nutrient availability).[60-63] Genetic variation in alcohol metabolism of both mother and fetus may also lead to differences in the susceptibility to develop alcohol-induced organ damage.[46,64,65]

The collective expression of consequences to the fetus from alcohol exposure is fetal alcohol spectrum disorder (FASD). The most specific and well-known consequence of alcohol exposure in utero is fetal alcohol syndrome (FAS), described in more detail below.

Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorder

There is no safe level of alcohol use during pregnancy. Complications from fetal alcohol exposure are called fetal alcohol spectrum disorders (FASD), characterized by neurodevelopmental impairment with or without facial dysmorphology, congenital anomalies and poor growth, and includes FAS, Partial Fetal Alcohol Syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects (ARBD), and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE). In individuals with FASD,

Alcohol exposure during pregnancy can have a profound impact on brain development in the fetus. This manifests as a range of symptoms in the baby and child and causes potential problems throughout the life course.

It is well established that prenatal alcohol exposure negatively affects many cognitive areas, including problems with learning, emotion, cognition, motor performance, perception, and behavior.

over 400 associated conditions have been identified, ranging from organ specific congenital malformations to mental and behavioral disorders including learning disabilities, attention deficit hyperactivity disorder (ADHD) and conduct disorders. In addition to medical problems, many social and economic difficulties can occur over the course of life. The extent of damage from drinking alcohol during pregnancy depends on factors such as how much was consumed, at what stage of pregnancy and for how long, the genetic makeup of both baby and mother, the mother's nutritional status and whether other substances were used.

The exact prevalence of the full range of FASD is not clear. Studies have estimated that 0.2 to 1.5 infants among every 1,000 live births have FAS.[66,67] Estimates across the full range of FASD are higher; different studies in the US have identified between 11 and 50 cases of FASD per 1,000 first grade students[68,69], and up to 98.5 cases per 1,000 children using a weighted approach.[69] In Europe, the estimated prevalence is 19.8 per 1,000 children.[70,71] These estimates are vastly higher than those reported in earlier studies[72,73], a reflection of how FASD continues to be a significant public health concern.

FASD has significant impacts on the economy and society as a whole. These include tangible expenses for substance abuse treatment, mental health services, foster care, the criminal justice system, and long-term care. The estimated lifetime cost for one person with FASD is around $2 million, encompassing medical care ($1.6 million) and productivity losses ($0.4 million).[74] The annual cost of FASD in Canada ranges from CAD1.3 billion to CAD2.3 billion, the highest contributor being productivity losses due to health issues and premature mortality.[75] Costs in Sweden have been estimated to €76,000 per child (0–17 years) and €110,000 per adult (18–74 years), corresponding to €1.6 billion per year[76], based on an estimated population prevalence of 0.2 per cent. The economic and social costs of FASD are no doubt large and variable. In order to better facilitate appropriate allocation of healthcare funding and supportive services into the future, it is crucial therefore that efforts to advance methods for estimating FASD prevalence and associated costs continue.

Range of neurocognitive problems

Many neurocognitive problems are associated with fetal alcohol exposure. These range from hyperactivity and attention deficit to learning disabilities to grave intellectual disability. A review of eight studies by the U.S. Centers for Disease Control and Prevention that included over 10,000 children aged 6 months to 14 years found that binge drinking during pregnancy was associated with the child having cognition-related problems.[77,78]

It is well established that prenatal alcohol exposure negatively affects many cognitive areas[79], including problems with learning, emotion, cognition, motor performance, perception, and behavior.[45] Cognitive and behavioral difficulties account for the majority of functional disabilities associated with FASD. While not everyone with FASD meets all the requirements for intellectual disability, many children (and adults) nevertheless experience cognitive problems that affect various aspects of their thinking. This includes a range of abilities and functions key to learning such as decision-making, memory, mathematics and comprehension, capacity for focus, and visual perception. In addition, problems such as poor social skills, inability to pay attention and poor impulse control can make it harder for them to do well or even meet minimum standards in school, at work, and sometimes, to live on their own. Moreover, prenatal alcohol exposure has a high comorbidity rate with other learning and behavioural disorders such as autism spectrum disorders and ADHD.[80-85]

Although no specific pattern of neurobehavioral deficits has been distinguished for FASD, some groups have attempted to identify constellations of impairments associated with prenatal alcohol exposure. As described below, three key problem areas include lower

intelligence quotient (IQ), fine and gross motor skill impairment, and attention deficit.

Lower IQ is one of the most reported findings in relation to prenatal alcohol exposure.[82] Estimates of average IQ scores for individuals with FAS range from about 68–79[86], while estimates for the full range of FASD fall within a much larger range of 20–120, with an average of about 72.[84,86] Among the population of affected children, overall ability levels are lowest among individuals with a diagnosis of FAS, followed by PFAS, and ARND.[87] However, intellectual deficits occur across the spectrum and children with and without FAS can exhibit below average IQ scores. The absence of typical facial features does not exclude impaired intellectual functioning.[83,88]

Motor skills can also be affected in people with prenatal alcohol exposure.[89,90] In adults with FASD, balance and fine motor control[89], as well as higher-order cognitive-motor abilities such as hand-eye coordination are affected.[91] Fine motor abilities may be more severely impacted[92], but studies tend to show that gross motor impairment is more common.[83,93]

Attention deficits are commonly associated with prenatal alcohol exposure and children with heavy prenatal alcohol exposure show both slower performance and attention problems.[94-97] Patterns and levels of attention deficits are not uniform, and processing of auditory information seems to be less affected than that presented visually.[98-101] Importantly, attention function measures can distinguish children with prenatal alcohol exposure from control children with a high degree of accuracy.[102] Overall, numerous studies have demonstrated the detrimental effect on attention abilities associated with in utero alcohol exposure and the potential benefit of using such measures to aid in identification of affected individuals. Multiple studies have compared children with FASD to those with attention-deficit/hyperactivity disorder (ADHD).[83]

Long-term behavioral and physical problems

FASD is more common among young people in foster care or involved with the justice and mental health systems. FASD has serious social and economic consequences, yet it often goes undiagnosed or

Attention deficits are commonly associated with prenatal alcohol exposure and children with heavy prenatal alcohol exposure show both slower performance and attention problems.

BOX 3 DEFICITS IN FASD

- **Executive Function** – Significant deficits in working memory, problem solving, planning, response inhibition
- **Verbal fluency** – Lower scores on verbal fluency, letter fluency, produce fewer words
- **Inhibition** – impairments in response inhibition (the ability to suppress one response in favor of another)
- **Problem solving and planning** – less time pre-planning their strategy before solving a problem, use less efficient strategies, show increased rule violations, and require more moves to solve a problem.
- **Concept formation and set-shifting** – deficits in detecting and producing concepts as well as poor cognitive flexibility
- **Language** – deficits in articulation, grammatical ability (especially specific to FASD), expressive and receptive skills, word ordering, sentence combining, and grammatical comprehension.

Source: Mattson et al. Alcohol Clin Exp Res. 2019 June ; 43(6): 1046–1062.[83]

** Medelvärdet av IQ i en befolkning är 100.*

unrecognized publicly. Diagnosis remains challenging because of limitations inherent to self-reported drinking (i.e. among biological parents), lack of biomarkers, and infrequency of diagnostic facial traits. Disagreement over diagnostic criteria and lack of diagnostic systems is a hindrance, but there are efforts to improve identification and management of FASD. These include studies of non-clinically-referred groups, studies of school-based populations, advanced 3D imaging of facial characteristics, and new screening tools.[103] However, even considering these difficulties, there is a plethora of evidence for severe long-term consequences accompanied by a significant societal and monetary cost.

Studies have found that adolescents and adults with fetal alcohol spectrum disorders face a range of adverse life outcomes. Eighty per cent experience difficulties living independently and being employed, 61% experience school disruptions, 50% have been confined (detention, prison, psychiatric or alcohol/drug inpatient). Average life expectancy is significantly lower (34 years) than in the general population. Among leading causes of death are suicide, accidents and alcohol or drug poisoning.[47]

Longitudinal cohort studies of FASD consistently show that serious adverse outcomes are more likely where support services are lacking. The complexity of parenting a child with FASD increases across adolescence and young adulthood. Caregivers of children with FASD experience increased burden, levels of stress and feelings of isolation. Moreover, the lifelong challenges and unmet needs of caregivers negatively affect family functioning and quality of life. Early recognition of FASD and early emphasis on prevention of secondary disabilities may decrease demands on families.

Summary

Alcohol is firmly established as a leading cause of acquired intellectual disability. At present, reviews conclude there is no level of alcohol consumption during pregnancy which is known to be safe.[104,105] FASD affects all strata of society, and confers enormous personal, social and economic effects across the lifespan.

3.2 Adolescent Brain and Development

Following birth, the brain continues to develop and mature, and is generally considered fully developed in the mid to late 20s. The prefrontal cortex, responsible for planning, prioritizing and decision making is the last part of the brain to mature. Adolescence is the phase of life between late childhood and early adulthood. In this life phase (sometimes defined as between 12–20 years of age) an adolescent experiences major changes in physical maturation including reaching maximum height and alterations in their brain and CNS. As a result of changes in their mental and emotional development, the adolescent may explore intimate relationships, self-identity, changes in self-perspective about the future, and a sense of independence, self-confidence, and self-control.

A major factor during the time associated with adolescent brain development is heightened risk-taking and extreme emotions. Risk behaviour (sometimes called "sensation-seeking behaviour") results in elevated risks to health and well-being, and is frequently linked to injuries. The most common causes of death for adolescents are motor vehicle accidents, other accident (e.g. falls, drownings), self harm and violence.[106]

The human brain is fully grown relatively soon after birth and the cerebral cortex soon reaches its maximum. However, structural imaging studies have shown[107-109] that grey matter matures from back to front such that maximum brain density is first reached by the grey matter, primarily the sensorimotor cortex where sensation and motor tasks reside. The higher functioning areas such as the dorsolateral prefrontal cortex, the inferior parietal gyrus, and the superior temporal gyrus are fully developed last, which includes higher cognitive functions such as behavioural control, planning, and assessing the risk of decisions. Autopsy findings suggest that these grey matter changes are due to synaptic pruning. Many synapses are formed in childhood that are later removed in adolescence[109], condensing the amount of synapses and increasing the effectivity.

Brain synapses that survive are likely the ones most being used. Even as the grey matter decreases in volume, the white matter which conducts neural information rapidly increases continually from childhood into early adulthood.[110] In short, the natural development and state of the brain during adolescence is one in which risk desirability and sensation seeking behaviour are often paramount.

Alcohol and the adolescent brain: A circular relationship

When alcohol is added to this natural process, high risk behaviour increases and more mature assessment of personal risk to self and others is decreased. Systematic research reviews find an ongoing interaction of adolescent brain development and neurological changes, exposure to alcohol via drinking, especially binge drinking, and present and future dysfunctions and illnesses for young adults and even older adults.

Tapert (2022)[111] has summarized the scientific research on alcohol's impact on adolescent and young adult brains as follows:

- Adolescent binge drinking is linked to a greater risk of more prominent grey matter reductions during adolescence.
- Drinking onset is associated with, and appears to precede, disrupted white matter integrity.
- Initiation of moderate to heavy alcohol use and incurring hangovers during adolescence may adversely influence neurocognitive functioning.
- Pronounced alcohol cue reactivity in heavy drinking teens, particularly in reaction to alcohol advertising materials.

A review of current research concludes that chronic alcohol exposure during critical developmental periods can create deficits in cognitive and related circuitry.[1] Alcohol

Systematic research reviews find an ongoing interaction of adolescent brain development and neurological changes, exposure to alcohol via drinking, especially binge drinking, and present and future dysfunctions and illnesses for young adults and even older adults.

These deficits are evident after exposure during every evaluated developmental window including prenatal, adolescent, and early/middle adulthood periods.

exposure was determined to have long-lasting detrimental effects on cognitive flexibility, with deficits in reversal learning (i.e. ability to actively supress or modulate behaviour to obtain a reward when reward rules change) being particularly marked. These deficits are evident after exposure during every evaluated developmental window including prenatal, adolescent, and early/middle adulthood periods. However, periods when neurological and cognitive-behavioural deficits appear are related to both the timing of alcohol exposure (age of first drink) as well as the developmental period of testing. For example, following adolescent alcohol exposure, prefrontal control of goal-directed over habit-based behaviours is reduced. This shift in cognitive flexibility is linked to decreased connectivity between different parts of the brain. Decreased connectivity between certain areas of the brain, in turn, can facilitate more alcohol consumption in adulthood, resulting in further cognitive decline – thus highlighting the cyclical and bidirectional relationship between alcohol use and cognition.[1]

Another review[112] summarizes the interaction between adolescence, biological sex, and exposure to stress and adolescent drinking. Neuroimaging studies have found reductions in Prefrontal Cortex (PFC) volume in adolescents with alcohol use disorder[113], especially in women.[114] Alterations in white matter microstructure during early adolescence have been associated with familial history of alcohol use and future instances of binge drinking.[115] Adolescents who went on to engage in binge drinking tended to have excessive maturation of connections between striatal regions (behavioural regulation) to the frontal cortex, but insufficient maturation of frontal lobe regions).[115]

Adolescent alcohol consumption also poses concern for present and future psychological illness.[116] In a study of nearly 500 000 Swedish men, Nordström et al (2013)[44] found binge drinking in adolescence to be the strongest risk factor for developing early onset dementia. Several longitudinal studies demonstrate that drinking alcohol in early adolescence predicts higher risk of alcohol use in late adolescence and early adulthood.[117-119] In addition, teenage alcohol consumption may indirectly predict higher incidences of Major Depressive Disorder (MDD) in later adulthood (e.g. late 20s to 30s). Magee and Connell (2021) for instance, described how teenage drinking can indirectly led to MDD via one of two pathways: (i) drinking at age 17 predicts alcohol use at age 22, which predicts higher risk of substance use at age 23, which leads to higher risk of MDD at age 30; (ii) alcohol use at age 17 predicts greater depressive symptoms at ages 22 and 23, which predicts greater risk of MDD diagnosis by age 30.[119]

Summary

In addition to the existing challenges posed by normal brain development, adolescent drinking can further increase the risk of harm such as injury and death from motor vehicle crashes, extreme sport and other competitive activities, conflict and violence, and self-harm including suicide. In some ways, the relationship between adolescent brain development and sensation seeking is further enhanced via drinking. In like manner, inherent natural risk behaviours can increase the desirability of alcohol, especially higher volume consumption and binge drinking as well as other drug use.

4 Alcohol and mental health, from young adulthood to middle-age

Mental health disorders are a major source of preventable mortality and morbidity. Global prevalence and reported disability adjusted life years for depressive disorders increase steeply after the second decade of life but continue to remain high throughout middle-age, particularly for women.[120]

The WHO describes depression as characterized by persistent sadness and lack of interest or pleasure in activities that were previously rewarding. Sleep disturbance, reduced or increased appetite, tiredness and poor concentration are also common and sometimes, depression may lead to suicide.[121,122] Depression is probably one of the most common mental health conditions in the general population with prevalence estimates ranging from around 17% (self-reported) to 5%–8% (clinical interview).[122,123] Along with anxiety-related disorders, population prevalence of depression appears to have increased substantially since the Covid-19 pandemic.[120]

In terms of contribution to the global burden of preventable injuries, suicide and self-harm rate second (to road injuries). Suicide is a major cause of premature death for people in their twenties[124] and it is estimated that more than 700 000 people die

from suicide each year.[125] Suicide can occur at any age but the age group 85+ has highest rate of suicide.[106] In Sweden, the male (16.9 per 100 000) suicide rate is more than double that for females (7.7 per 100 000).[126]

4.1 Alcohol and depression

There is a long standing, common recognition that heavy drinking and depression are related, with epidemiological and clinical studies suggesting close linkages between the two disorders. The nature of the causal connection is, however, complicated and often described as a classic "chicken-egg problem". Although debate continues, over time, research evidence has increasingly come to favour heavy drinking as the primary condition, with depression as a secondary consequence. Contributing to the causal role in the aetiology of depression are the effects of alcohol misuse on an individual's social, economic and legal circumstances. In addition, other potential mechanisms underlying these causal linkages include neurophysiological and metabolic changes resulting from exposure to alcohol.[127]

The view that drinking and depression are related has been reinforced by recent observational studies. Systematic reviews by Puddephatt et al. (2022)[128] and Li et al. (2020)[129] and a recent cohort study (Hammerton et al. 2023)[130] concur that alcohol dependence and depression are strongly related. Indeed, it has been estimated that people with a mood disorder are twice as likely to have a concurrent alcohol use disorder (AUD). Moreover, a dose-response relationship whereby risk of depression is highest for the most severe form of AUD, lower for more mild forms of AUD and not found at all for alcohol consumption without AUD has been demonstrated.[128] Notably, many of the same studies also find no association between heavy or binge drinking and depressive symptoms. This raises the question of the nature of alcohol dependence and its diagnosis. What is dependence other than harmful levels of consumption? In an influential critique of the diagnostic system, Rehm and colleagues found that criteria for the diagnosis of alcohol dependence (ICD-10 or DSM5) are all caused by *heavy drinking*.[131]

In another series of observational studies, researchers have looked for effects of moderate drinking on risk of depression. Various recent reviews (e.g. [132-134]) including studies of Swedish populations (e.g. [135]), have found that compared to non-drinkers, low-to-moderate level drinkers are less likely to suffer depression. In keeping with this, probably the largest review to date (111 articles), reported that moderate drinkers appeared to have lower rates of depression than non-drinkers and heavy drinkers.[132] However, as the authors were careful to clarify, problems such as residual confounding and especially, the "sick quitter" phenomenon are very common to this observational literature and may well explain apparent benefits. Related to this, another problem common to the observational literature is "reverse causation" whereby the direction of the causal effect is,

in actuality, opposite to what was proposed by the study. In simple terms, rather than stopping drinking causing depression, mental disease, including depression, might lead people to stop drinking. Studies which have investigated whether treatment for alcohol problems leads to a reduction in depressive symptoms suggest this is likely the case. A meta-analysis of five studies of interventions targeting excessive alcohol use found significant reductions in depression symptoms[136] and a recent longitudinal study showed decreases in the number of alcoholic drinks per week, as well as abstinence, led to a reduction in depressive symptoms.[137] Finally, a recent study[138] specifically tested for reverse causation as an explanation for observed J-shaped curves for alcohol and depression using a reverse Mendelian randomization approach. They showed that people with a genetic susceptibility to depression were more likely to drink alcohol, but, these same people were also more likely to stop drinking and become ex-drinkers. The study's findings strongly point to reverse causation and the sick quitter hypothesis (i.e. misclassification error) as responsible for apparent benefits of low-to-moderate drinking among conventional observational studies.

(See Box 2 for a more detailed explanation of residual confounding and misclassification error in observational studies).

4.2 Alcohol and suicide

Evidence for a causal relationship between alcohol and suicide is strong and GBD data estimate that around 15% of suicides are caused by alcohol.[25] As evidenced by a series of systematic reviews, alcohol use increases suicide risk both acutely and chronically. Acutely, alcohol can increase impulsivity leading to suicide, i.e. heavy drinking in-the-event increases suicide risk (e.g. [139]). Chronically, long-term dependent drinking increases the risk of suicide as a consequence of increased rates of depression (e.g. [140]). In a recent meta-analysis of 33 studies, Isaacs et al (2022)[141] reported a 94% increase in the risk of death by suicide among alcohol users compared with abstainers. Moreover, there is some evidence that in a dose-response manner and up to a certain point (probably where motor coordination becomes seriously affected, e.g. ≥0.40 g/dL), alcohol intoxication increases the likelihood that a firearm (or other violent method) will be used as the method of suicide.[142,143]

Population level studies that relate per capita alcohol consumption to suicide prevalence or evaluate effectiveness of polices aimed at reducing consumption also provide evidence for a strong link between alcohol and suicide. In a study of Swedish data, Norström and Ramstedt (2018)[144] reported a 13% increase in suicides per litre increase in (pure) alcohol consumed. In the USA, the relationship appears to be less strong with an estimated 2.3% increase in suicide risk per litre of alcohol consumed.[145] Also in the USA, almost 30% of adolescent males with FASD reported a serious suicide attempt – more than 19 times higher than the national average.[146] A systematic literature review by Kõlves et al. (2020)[147] showed that, in most cases, policy which reduced alcohol's physical availability or increased the cost of alcohol, led to a reduction in suicides across Europe and the US. In line with this, Xuan et al's (2016)[148] review of 17 studies demonstrated that restrictive alcohol policies contribute to suicide prevention at the general population level and to a reduction of alcohol involvement among suicide deaths.

Summary

Alcohol use, especially heavy use, and mental health are closely connected. Having an alcohol use disorder (regular harmful use of alcohol) increases the risk of depression and both acute and chronic heavy drinking increase the risk of suicide. Reported protective effects of low-to-moderate drinking on risk of depression are unlikely to be causal.

Alcohol use, especially heavy use, and mental health are closely connected. Having an alcohol use disorder (regular harmful use of alcohol) increases the risk of depression and both acute and chronic heavy drinking increase the risk of suicide.

5 The ageing brain

For the ageing brain, alcohol presents some unique challenges. Ageing heralds the onset of previously unexperienced chronic health conditions, impaired vision, hearing and balance problems, muscle weakness, social isolation, increased medication use and a general decline in regenerative potential. When common age-related declines in physical and neurological functioning converge with decades of alcohol exposure, they can bring unexpected and debilitating consequences. As decades pass, most people will change how much and how often they consume alcohol. Generally speaking, drinkers tend to reduce their average alcohol consumption as they age. Some who were once heavy drinkers in their 20s and 30s may become abstinent later in life. It is interesting then that from some countries, including Sweden, there is recent evidence of a trend towards increasing levels of average use and/or heavy drinking among older age groups compared to previous cohorts.[149-153] Since a range of prevalent conditions that occur in older age are either attributable to or exacerbated by alcohol exposure, more widespread use or increasing prevalence of heavy use may have direct social and economic consequences. This section summarises evidence for alcohol's relationship to a selection of three conditions of particular concern to older people: dementia, stroke and falls.

5.1 Alcohol and dementia

Dementia is a general term for a range of neurodegenerative diseases that affect the brain's ability to remember, process information and learn. The effects of dementia go beyond that expected with normal ageing and undermine an individual's ability to undertake every-day activities, communicate with others and to respond appropriately to their environment.

Dementia ranks fifth among causes of death world-wide[154] and as of yet, there are few effective treatment options. It has been predicted that as populations age and detection and diagnosis improve, dementia cases will triple over the next three decades.[155]

As such, among efforts key to address dementia and its associated social costs, reducing population exposure to potentially modifiable risk factors is considered paramount.[156] As a condition that can lead to severe neurodegeneration (especially in later stages), patients often require intense care, the global financial and social costs of which are considerable. Wimo et al (2023)[157] estimated the annual global costs of dementia at USD 1.3 Trillion (for 55.2 million people with dementia) with 16% going to medical costs, 34% to social sector costs, and 50% to informal care. A Swedish study estimated that in 2012, social costs of dementia were approximately SEK 398,000 per person with dementia – about SEK 520,000 or USD

When common age-related declines in physical and neurological functioning converge with decades of alcohol exposure, they can bring unexpected and debilitating consequences.

Notably, for all types of dementia, heavy alcohol use has been identified as the strongest modifiable risk factor for disease onset and is associated with all other independent risk factors.

47,000 in today's dollars – and that about 60% of the total national cost was attributable to institutional care.[158]

There are many different forms of dementia including alcoholic dementia, vascular dementia, dementia with Lewy bodies, and frontotemporal dementias; however, Alzheimer's disease is the most common and accounts for 60%–70% of cases.[159] Alzheimer's disease generally occurs among people in their mid-60s or older, but about one in ten cases will occur among younger people (i.e. "early-onset dementia") – even before middle age in rare cases.[159] The biggest risk factor for dementia is ageing but a range of other potential causes and risk factors have been identified, including (but not limited to) overweight, diabetes, tobacco use, poor diet, lack of exercise, high blood pressure, and genetic markers.

Several plausible biological mechanisms may explain alcohol's role in raising dementia risk. Cumulative direct effects such as brain cell death brought about by exposure to neurotoxic effects of alcohol metabolites such as acetaldehyde or activation of inflammatory processes that compromise brain structure and function are probable. In addition to or alternatively, more indirect effects such as alcohol's role in promoting thiamine deficiency[4] or in elevating blood pressure in connection with vascular dementia[160] may play a key role. Some forms of dementia specifically involve diagnosis of an underlying alcohol use disorder and may be broadly referred to as "alcohol-related dementia" (e.g. alcoholic dementia, Korsakoff's psychosis).[161] For these conditions, diagnoses directly establish that the patient's brain has been injured by long-term heavy alcohol use, however, in terms of disease expression, alcohol-related dementia is not easily distinguished from Alzheimer's disease. Notably, for all types of dementia, heavy alcohol use has been identified as the strongest modifiable risk factor for disease onset (especially early onset, i.e. <65yrs) and is associated with all other independent risk factors.[162,163] An important Swedish study conducted on men conscripted for mandatory military service found that a history of being treated in hospital for alcohol intoxication during adolescence was the most important risk factor for vascular, unspecified and alcoholic dementia diagnosed before the age of 65 (early onset).[44]

Most, but not all (e.g. [164]), recent reviews and meta-analyses of observational studies agree that heavy alcohol use increases risk of dementia, including early onset dementia.[162,165-170] However, many of these same meta-analyses have also found that at lower doses, alcohol use appears to reduce dementia risk. For example, drawing on data from seven European studies Kilian et al (2023)[166] found that compared to non-drinkers, heavy drinkers (i.e. at least 24g of pure alcohol per day) had higher risk of mild cognitive impairment and dementia, whereas low to moderate level drinkers (i.e. <= 24g per day) had lower risk of dementia compared to current abstainers.

There are many reasons to suspect that findings of protection from dementia associated with low-dose alcohol consumption (i.e. J-shaped or U-shaped curves) are spurious. Across the board, reviewers have noted significant methodological problems with the non-randomized observational studies that form the bulk of studies on alcohol and dementia (e.g. [168]). Frequently cited limitations include inconsistent measurement of alcohol use and/or dementia, poor control of potential confounders such as socio-economic status, and insufficient attention to participant attrition effects in heavy drinker populations. Notably, under-representation of heavy drinkers in study populations is common, and people with alcohol use disorders have substantially lower life expectancies (24–28 fewer years) compared to their low and moderate drinking counterparts).[171] Another important consideration is "reverse causation". As people acquire dementia, they drink less and less alcohol or may stop drink-

ing. In pre-clinical stages of dementia (i.e. before it has been appreciated or diagnosed), continued low-volume alcohol consumption may therefor *reflect* better cognitive function, rather than causing better cognitive function.

Moreover, as discussed in Box 2, studies which fail to identify ex-drinkers among (current) non-drinker groups or adopt appropriate intention-to-treat approaches are vulnerable to misclassification error and bias. It has been shown for instance that ex-drinkers have a 20–60% higher risk of dementia compared to moderate current drinkers[172] and that when ex-drinkers are removed from non-drinker comparison groups, apparent protective effects for dementia among moderate drinkers are reduced.[173] Moreover, rather than assessing lifetime drinking trajectories that begin during youth, the vast majority of observational studies are limited to assessing recent past or current drinking levels among participants who have already reached their older years. This methodological limitation leaves open the strong possibility of selection bias.[174] Somewhat countering findings of protection among observational studies, Mendelian randomization studies (which are less prone to selection bias and reverse causation) have shown mixed results, but no evidence overall that low and moderate level drinkers have reduced risk of dementia.[175-177] In fact, results from the Andrews et al

Alcohol use and brain structure have a negative linear association (i.e. more lifetime alcohol consumption, less brain).

(2020)[176] study suggest that low to moderate level drinking is associated with earlier age of onset for Alzheimer's disease.

Finally, recent large-scale neuroimaging studies (i.e. MRI) of general populations consistently show that alcohol use and brain structure have a negative linear association (i.e. more lifetime alcohol consumption, less brain). At any level of consumption, reductions in grey and white matter volume and in white matter cortical thickness and microstructure are widely apparent throughout the brain[4] and particularly the hippocampus (an area of the brain associated with memory).[178] These findings concur with experimental studies that have applied well validated mouse-models and show that, even at low-to-moderate levels, regular alcohol use can promote both behavioral and neurological pathology in mice with pre-clinical Alzheimer's disease (e.g. [179-181]). On the whole, as the capability of neuroimaging and experimental lab studies has increased, putative arguments regarding biological mechanisms for low-to-moderate dose alcohol protection on dementia risk have become increasingly implausible.

5.2 Alcohol and stroke

Stroke is a condition that predominantly (but not exclusively) affects older people. Strokes can be either ischemic or hemorrhagic in nature. Ischemic strokes are the most common and they occur when blood flow to the brain is blocked or reduced. Hemorrhagic stroke also involves interrupted blood flow but arises from a burst blood vessel that can also create pressure on surrounding tissue. In addition to premature death, stroke entails considerable morbidity, much of which occurs in older age when people are more vulnerable to long-lasting debilitation and slow recovery requiring considerable health care resources. In both Europe and the USA, stroke is the leading neurological disease in terms of disability adjusted life years[182,183] and the financial burden of stroke on health services and societies is very large (e.g. for USA about USD 103 Billion).[184]

Observational and Mendelian randomization studies concur that drinking above low-to-moderate levels, whether regular or episodic (binge drinking in particular), is a risk factor for both ischemic and hemorrhagic stroke.[11] One of the main mechanisms for this is that alcohol use can raise blood pressure, and elevated blood pressure is the most important major risk factor for stroke.[160]

Past reviews and meta-analyses of observational studies have also found that low level alcohol use is protective for ischemic (but not hemorrhagic) stroke. Apparent protection is found for both men and women and occurs at a very low levels of use, i.e. less than one drink per day for men and about one drink per day for women.[185,186] However, as described above for dementia, the non-random nature of observational studies makes them prone to various sources of bias and residual confounding which can influence the outcome. Because alcohol use can change considerably over a lifetime and tends to decrease with increasing age, frailty and ill-health, bias that works in favour of finding protective effects can readily occur when selecting study participants and classifying participant exposure.[174] It is notable therefore, that three large observational studies which conscientiously separated former drinkers from never drinkers in their analyses found no evidence that low to moderate drinking in middle-age protects against stroke.[10,187,188] What's more, Mendelian randomization studies, which are not subject to the same sources of bias as observational studies, find no evidence that low level alcohol use is protective for stroke.[189,190]

5.3 Alcohol and falls

Older people fall more often than their younger counterparts. World-wide, falls are a major contributor to morbidity and mortality and ranked 8th for people aged 75 years and older as a cause of age-standardized disability

adjusted life years.[191] For older people, falls are the leading cause of injury-related death.[192] Fall-related injuries currently pose major healthcare costs given their high incidence and long recovery times and are set to increase substantially as populations age.

Pooled data from emergency department studies across 28 countries showed that both frequent and binge drinking are strong predictors of alcohol-involved falls.[193] A meta-analysis of five studies that measured drinking-in-the-event of a fall found a pronounced dose-response relationship such that for each 10g of alcohol consumed, the likelihood of a fall increased by 15%.[23] For older people specifically, results from an experimental study suggested that even low level alcohol use adversely affects postural stability among those aged over 65 years, and the effect was particularly notable for those who already have poor balance.[194] Two Scandinavian studies, one from Sweden[195] and one from Norway[196] confirmed that heavier alcohol use in older age increases fall risk. In the Norwegian study, risk of fall injuries among those aged 60 years and older was over ten times greater among participants who reported drinking to intoxication at least monthly.

There are a range of reasons why falls are more likely to occur when the brain has been exposed to alcohol. Even at low to moderate levels, experimental studies have established that alcohol affects balance, visual focus and reaction time.[25] Neuroimaging studies also confirm that alcohol directly impairs the function of the cerebellum (which regulates balance) and the cerebral cortex (responsible for processing new information). Impairment of these brain structures can lead to dizziness, staggering, and reduced ability to pay attention to environmental hazards.[25] For older drinkers, physical changes that accompany ageing such as reduced alcohol tolerance due to less body fluid, slower liver function, medication use and impaired balance or confusion suggest heightened susceptibility

to psycho-motor impairments attributed to alcohol.[197-200] If regular heavy alcohol use over the lifespan is implicated, then some degree of cognitive impairment or dementia is likely and several studies have shown dementia to increase the risk of falling.[201-203] Peripheral neuropathy, which affects gait and balance is also more likely among heavy drinkers and may predispose older drinkers to falls.

Summary

For the ageing brain, alcohol use – particularly drinking above low levels – is a key risk factor for three neurological or neurologically-mediated conditions that are often lethal or otherwise disabling: dementia, stroke and falls.

There are a range of reasons why falls are more likely to occur when the brain has been exposed to alcohol. Even at low to moderate levels, experimental studies have established that alcohol affects balance, visual focus and reaction time.

6 Summary, conclusions and recommendations

Alcohol is a leading, modifiable threat to the human brain and to overall physical health. The range of neurological diseases to which alcohol can cause or contribute is staggering: developmental delay, learning disabilities, attention deficit hyperactivity disorder, alcohol use disorder, depression, stroke, dementia, traumatic brain injuries and seizure disorders, among others. Similarly, the number of non-neurological conditions that may be mediated through alcohol's acute or chronic effect on the brain are also staggering: poisonings and overdoses, suicide and homicide, falls, sexual assaults, car crashes and so on.

Were these problems caused by a substance other than alcohol, it is difficult to imagine that the toll on human health and society would be quite so overlooked and/or tolerated. Raising individual-level knowledge of these connections can help ensure that these relationships are understood and appreciated for their scope and magnitude. We hope that this report is useful in that regard.

But individual-level awareness and even internally motivated change in some people are unlikely to yield significant change in Sweden or other nations with similarly embedded social, economic and political attachments to the sale and consumption of alcohol. To achieve significant change, alcohol consumption would need to decrease nationally. Interventions are needed that can reduce average consumption, heavy use and binge drinking (i.e. drinking to the point of impairment). Fortunately, since alcohol is a legal product that is to be regulated by government, such interventions exist in the form of public alcohol control policies. Of these, the most effective raise or maintain higher prices for alcohol, limit convenience of access, and restrict marketing and advertising of alcohol products. Reductions in general population alcohol consumption are primarily achieved through reduced drinking among the heaviest consumers but also among those who binge drink but who otherwise consume "moderate" amounts of alcohol in total. We therefore recommend, that in order to improve brain health of their populations, elected representatives strive to introduce policies that reduce affordability, availability and acceptability of alcohol.

While screening and appropriate interventions for those identified with hazardous alcohol use may work in some cases, practitioners need more incentives, training, and specialist support for these to be implemented more widely and effectively. Alcohol is often neglected in primary prevention and is viewed by practitioners and their patients as less important than regular exercise, diet and not smoking.

Alcohol policy interventions

To reduce alcohol's impact and harmful effects on human cognition across the life course, it is important to have policies which restrict total alcohol consumption. The principal ways in which this can be achieved is through reducing alcohol's affordability, availability and acceptability. There are some evidence-based strategies to achieve these objectives:

- **Reducing affordability:** this can be achieved through pricing and taxation strategies. It is the amount of ethanol in alcoholic beverages that leads directly to harm and so taxes are best applied to the volume of ethanol in an alcoholic drink. In addition, heavier drinkers tend to choose the cheapest alcohol. Setting policies that raise or maintain high minimum or floor prices are effective at reducing consumption and related harms.
- **Reducing availability:** restrictions on the hours and days of sale, the density of liquor outlets and on access to alcohol by those under legal drinking age are proven ways to reduce or maintain lower alcohol consumption in the general population. Maintenance of government alcohol monopolies such as Systembolaget in Sweden can be one mechanism to manage and prevent increased population consumption.
- **Reducing acceptability:** restrictions on the marketing and advertising of alcohol may be effective in reducing its acceptability and consumption, especially among adolescents and young adults. Labelling alcohol containers with health warnings e.g. cancer risks may increase public support for the above policies designed to reduce alcohol's affordability and availability. If labels are designed well they may also have direct impacts on population levels of alcohol use.[204]

To achieve significant change, alcohol consumption would need to decrease nationally. Interventions are needed that can reduce average consumption, heavy use and binge drinking (i.e. drinking to the point of impairment).

References

1. Dannenhoffer, C. A., Robertson, M. M., Macht, V. A., Mooney, S. M., Boettiger, C. A., & Robinson, D. L. (2021). Chronic alcohol exposure during critical developmental periods differentially impacts persistence of deficits in cognitive flexibility and related circuitry. In *International Review of Neurobiology* (Vol. 160, pp. 117–173). Elsevier. https://doi.org/10.1016/bs.irn.2021.07.004

2. Pérez-García, J. M., Suárez-Suárez, S., Doallo, S., & Cadaveira, F. (2022). Effects of binge drinking during adolescence and emerging adulthood on the brain: A systematic review of neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 137*, 104637. https://doi.org/10.1016/j.neubiorev.2022.104637

3. Wolfe, M., Menon, A., Oto, M., Fullerton, N. E., & Leach, J.-P. (2023). Alcohol and the central nervous system. *Practical Neurology, 23*(4), Article 4. https://doi.org/10.1136/pn-2023-003817

4. Nutt, D., Hayes, A., Fonville, L., Zafar, R., Palmer, E. O. C., Paterson, L., & Lingford-Hughes, A. (2021). Alcohol and the Brain. *Nutrients, 13*(11), Article 11. https://doi.org/10.3390/nu13113938

5. Kesserwani, H. (2021). Migraine Triggers: An Overview of the Pharmacology, Biochemistry, Atmospherics, and Their Effects on Neural Networks. *Cureus*. https://doi.org/10.7759/cureus.14243

6. Hu, N., Ma, Y., He, J., Zhu, L., & Cao, S. (2020). Alcohol consumption and incidence of sleep disorder: A systematic review and meta-analysis of cohort studies. D*rug and Alcohol Dependence, 217*, 108259. https://doi.org/10.1016/j.drugalcdep.2020.108259

7. Kiss, O., Goldstone, A., de Zambotti, M., Yüksel, D., Hasler, B. P., Franzen, P. L., Brown, S. A., De Bellis, M. D., Nagel, B. J., Nooner, K. B., Tapert, S. F., Colrain, I. M., Clark, D. B., & Baker, F. C. (2023). Effects of emerging alcohol use on developmental trajectories of functional sleep measures in adolescents. *SLEEP*, zsad113. https://doi.org/10.1093/sleep/zsad113

8. Meyrel, M., Rolland, B., & Geoffroy, P. A. (2020). Alterations in circadian rhythms following alcohol use: A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 99*, 109831. https://doi.org/10.1016/j.pnpbp.2019.109831

9. Cheng, C., Huang, C.-L., Tsai, C.-J., Chou, P.-H., Lin, C.-C., & Chang, C.-K. (2017). Alcohol-Related Dementia: A Systemic Review of Epidemiological Studies. *Psychosomatics, 58*(4), Article 4. https://doi.org/10.1016/j.psym.2017.02.012

10. Smyth, A., O'Donnell, M., Rangarajan, S., Hankey, G. J., Oveisgharan, S., Canavan, M., McDermott, C., Xavier, D., Zhang, H., Damasceno, A., Avezum, A., Pogosova, N., Oguz, A., Ryglewicz, D., Iversen, H. K., Lanas, F., Rosengren, A., Yusuf, S., Langhorne, P., & on behalf of the INTERSTROKE Investigators. (2023). Alcohol Intake as a Risk Factor for Acute Stroke: The INTERSTROKE Study. *Neurology, 100*(2), Article 2. https://doi.org/10.1212/WNL.0000000000201388

11. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2019). *Alcohol and older people* (Alcohol and Society). Swedish Society of Medicine, Swedish Society of Nursing, CERA & IOGT-NTO.

12. Fekjaer, H. O. (2013). Alcohola universal preventive agent? A critical analysis. *Addiction (Abingdon, England), 108*(12), 2051–2057. https://doi.org/10.1111/add.12104

13. Naimi, T. S., Brown, D. W., Brewer, R. D., Giles, W. H., Mensah, G., Serdula, M. K., Mokdad, A. H., Hungerford, D. W., Lando, J., Naimi, S., & Stroup, D. F. (2005). Cardiovascular risk factors and confounders among nondrinking and moderate drinking U.S. adults. *American Journal of Preventive Medicine, 28*(4), 369–373. https://doi.org/10.1016/j.amepre.2005.01.011

14. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2014). *The Effects of Low-dose Alcohol Consumption* (Alcohol and Society, pp. 6–23). http://urn.kb.se/resolve?urn=urn:nbn:se:iogt-2014-aos-en

15. Liang, W., & Chikritzhs, T. (2013). Observational research on alcohol use and chronic disease outcome: New approaches to counter biases. *TheScientificWorldJournal, 2013*, 860915. https://doi.org/10.1155/2013/860915

16. Zhao, J., Stockwell, T., Roemer, A., Naimi, T., & Chikritzhs, T. (2017). Alcohol Consumption and Mortality From Coronary Heart Disease: An Updated Meta-Analysis of Cohort Studies. *Journal of Studies on Alcohol and Drugs, 78*(3), Article 3. https://doi.org/10.15288/jsad.2017.78.375

17. Naimi, T. S., Stockwell, T., Zhao, J., Xuan, Z., Dangardt, F., Saitz, R., Liang, W., & Chikritzhs, T. (2017). Selection biases in observational studies affect associations between 'moderate' alcohol consumption and mortality. *Addiction (Abingdon, England), 112*(2), 207–214. https://doi.org/10.1111/add.13451

18. Sattar, N., & Preiss, D. (2017). Reverse Causality in Cardiovascular Epidemiological Research: More Common Than Imagined? *Circulation, 135*(24), 2369–2372. https://doi.org/10.1161/CIRCULATIONAHA.117.028307

19. Holder, H., Chikritzhs, T., Naimi, T., Andréasson, S., & Stockwell, T. (2013). *Alcohol and Society: Youth and young adults* (Alcohol and Society). IOGT-NTO, Swedish Society of Medicine.

20. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2015). *Second-hand effects of alcohol consumption* (Alcohol and Society).

21. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2017). *Alcohol and violence* (Alcohol and Society).

22. Martin, T. L., Solbeck, P. A. M., Mayers, D. J., Langille, R. M., Buczek, Y., & Pelletier, M. R. (2013). A Review of Alcohol-Impaired Driving: The Role of Blood Alcohol Concentration and Complexity of the Driving Task. J*ournal of Forensic Sciences, 58*(5), Article 5. https://doi.org/10.1111/1556-4029.12227

23. Taylor, B., Irving, H. M., Kanteres, F., Room, R., Borges, G., Cherpitel, C., Greenfield, T., & Rehm, J. (2010). The more you drink, the harder you fall: A systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. *Drug and Alcohol Dependence, 110*(1–2), Article 1–2. https://doi.org/10.1016/j.drugalcdep.2010.02.011

24. Irwin, C., Iudakhina, E., Desbrow, B., & McCartney, D. (2017). Effects of acute alcohol consumption on measures of simulated driving: A systematic review and meta-analysis. *Accident; Analysis and Prevention, 102*, 248–266. https://doi.org/10.1016/j.aap.2017.03.001

25. Chikritzhs, T., & Livingston, M. (2021). Alcohol and the Risk of Injury. *Nutrients, 13*(8), Article 8. https://doi.org/10.3390/nu13082777

26. Dawson, D., & Reid, K. (1997). Fatigue, alcohol and performance impairment. *Nature, 388*(6639), Article 6639. https://doi.org/10.1038/40775

27. Zoethout, R. W. M., Delgado, W. L., Ippel, A. E., Dahan, A., & van Gerven, J. M. A. (2011). Functional biomarkers for the acute effects of alcohol on the central nervous system in healthy volunteers. *British Journal of Clinical Pharmacology, 71*(3), 331–350. https://doi.org/10.1111/j.1365-2125.2010.03846.x

28. Bjork, J. M., & Gilman, J. M. (2014). The effects of acute alcohol administration on the human brain: Insights from neuroimaging. *Neuropharmacology, 84*, 101–110. https://doi.org/10.1016/j.neuropharm.2013.07.039

29. Jacob, A., & Wang, P. (2020). Alcohol Intoxication and Cognition: Implications on Mechanisms and Therapeutic Strategies. *Frontiers in Neuroscience, 14*, 102. https://doi.org/10.3389/fnins.2020.00102

30. WHO. (2018, September 6). *GHO | By category | Regional prevalence, AAFs (15+), road traffic crash deaths – By WHO region*. WHO; World Health Organization. https://apps.who.int/gho/data/view.main.A1082v

31. Borges, G., Cherpitel, C., Orozco, R., Bond, J., Ye, Y., Macdonald, S., Rehm, J., & Poznyak, V. (2006). Multicentre study of acute alcohol use and non-fatal injuries: Data from the WHO collaborative study on alcohol and injuries. *Bulletin of the World Health Organization, 84*(6), 453–460. https://doi.org/10.2471/blt.05.027466

32. Kassym, L., Kussainova, A., Semenova, Y., Kussainov, A., Marapov, D., Zhanaspayev, M., Urazalina, Z., Akhmetova, A., Tokanov, M., Smail, Y., & Bjørklund, G. (2023). Worldwide Prevalence of Alcohol Use in Non-Fatally Injured Motor Vehicle Drivers: A Systematic Review and Meta-Analysis. *Healthcare (Basel, Switzerland), 11*(5), Article 5. https://doi.org/10.3390/healthcare11050758

33. Høye, A. K., & Storesund Hesjevoll, I. (2023). Alcohol and driving—How bad is the combination? A meta-analysis. *Traffic Injury Prevention, 24*(5), Article 5. https://doi.org/10.1080/15389588.2023.2204984

34. WHO. (2018). *Global status report on alcohol and health 2018*. World Health Organization. https://iris.who.int/handle/10665/274603

35. Moskowitz, H., & Fiorentino, D. (2000). *A Review of the Scientific Literature Regarding the Effects of Alcohol on Driving-Related Behavior at blood alcohol concentrations of 0.08 grams per deciliter and lower* (Final Report DOT HS 809 028). U.S.Department of Transportation, National Highway Traffic Safety Administration.

36. Rezaee-Zavareh, M. S., Salamati, P., Ramezani-Binabaj, M., Saeidnejad, M., Rousta, M., Shokraneh, F., & Rahimi-Movaghar, V. (2017). Alcohol consumption for simulated driving performance: A systematic review. *Chinese Journal of Traumatology, 20*(3), Article 3. https://doi.org/10.1016/j.cjtee.2017.04.002

37. Ogden, E. J. D., & Moskowitz, H. (2004). Effects of alcohol and other drugs on driver performance. *Traffic Injury Prevention, 5*(3), 185–198. https://doi.org/10.1080/15389580490465201

38. Jones, A. (2022). How Nordic Countries Enforce Impaired Driving Legislation. *Forensic Science Review, 34*(2), 131–143.

39. Exum, M. L. (2006). Alcohol and aggression: An integration of findings from experimental studies. *Journal of Criminal Justice, 34*(2), Article 2. https://doi.org/10.1016/j.jcrimjus.2006.01.008

40. Abbey, A., Wegner, R., Woerner, J., Pegram, S. E., & Pierce, J. (2014). Review of Survey and Experimental Research That Examines the Relationship Between Alcohol Consumption and Men's Sexual Aggression Perpetration. *Trauma, Violence, & Abuse, 15*(4), 265–282. https://doi.org/10.1177/1524838014521031

41. Attwood, A. S., & Munafò, M. R. (2014). Effects of acute alcohol consumption and processing of emotion in faces: Implications for understanding alcohol-related aggression. *Journal of Psychopharmacology (Oxford, England), 28*(8), Article 8. https://doi.org/10.1177/0269881114536476

42. Crane, C. A., Godleski, S. A., Przybyla, S. M., Schlauch, R. C., & Testa, M. (2016). The Proximal Effects of Acute Alcohol Consumption on Male-to-Female Aggression: A Meta-Analytic Review of the Experimental Literature. *Trauma, Violence & Abuse, 17*(5), Article 5. https://doi.org/10.1177/1524838015584374

43. Reay, A. M., & Browne, K. D. (2001). Risk factor characteristics in carers who physically abuse or neglect their elderly dependants. *Aging & Mental Health, 5*(1), Article 1. https://doi.org/10.1080/13607860020020654

44. Nordström, P., Nordström, A., Eriksson, M., Wahlund, L.-O., & Gustafson, Y. (2013). Risk factors in late adolescence for young-onset dementia in men: A nationwide cohort study. *JAMA Internal Medicine, 173*(17), Article 17. https://doi.org/10.1001/jamainternmed.2013.9079

45. Caputo, C., Wood, E., & Jabbour, L. (2016). Impact of fetal alcohol exposure on body systems: A systematic review. *Birth Defects Research. Part C, Embryo Today: Reviews, 108*(2), Article 2. https://doi.org/10.1002/bdrc.21129

46. Terasaki, L. S., Gomez, J., & Schwarz, J. M. (2016). An examination of sex differences in the effects of early-life opiate and alcohol exposure. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 371*(1688), Article 1688. https://doi.org/10.1098/rstb.2015.0123

47. Popova, S., Charness, M. E., Burd, L., Crawford, A., Hoyme, H. E., Mukherjee, R. A. S., Riley, E. P., & Elliott, E. J. (2023). Fetal alcohol spectrum disorders. *Nature Reviews Disease Primers, 9*(1), Article 1. https://doi.org/10.1038/s41572-023-00420-x

48. Seemiller, L. R., & Gould, T. J. (2020). The effects of adolescent alcohol exposure on learning and related neurobiology in humans and rodents. *Neurobiology of Learning and Memory, 172*, 107234. https://doi.org/10.1016/j.nlm.2020.107234

49. Hua, J. P. Y., Sher, K. J., Boness, C. L., Trela, C. J., McDowell, Y. E., Merrill, A. M., Piasecki, T. M., & Kerns, J. G. (2020). Prospective Study Examining the Effects of Extreme Drinking on Brain Structure in Emerging Adults. *Alcoholism, Clinical and Experimental Research, 44*(11), 2200–2211. https://doi.org/10.1111/acer.14446

50. Linden-Carmichael, A. N., Mogle, J., & Miller, S. E. (2023). Associations between black-out drinking and self-reported everyday cognition among young adults. *Addictive Behaviors, 141*, 107653. https://doi.org/10.1016/j.addbeh.2023.107653

51. Raninen, J., Larm, P., Svensson, J., Livingston, M., Sjödin, L., & Karlsson, P. (2021). Normalization of Non-Drinking? Health, School Situation and Social Relations among Swedish Ninth Graders That Drink and Do Not Drink Alcohol. International *Journal of Environmental Research and Public Health, 18*(21), Article 21. https://doi.org/10.3390/ijerph182111201

52. Whatnall, M., Ashton, L., Patterson, A., Smith, J., Duncan, M., Burrows, T., Kay-Lambkin, F., & Hutchesson, M. (2022). Are health behaviors associated with academic performance among tertiary education students? A systematic review of cohort studies. *Journal of American College Health*, 1–13. https://doi.org/10.1080/07448481.2022.2063024

53. Garduno, A. C., Laughlin, G. A., Bergstrom, J., Tu, X. M., Cummins, K. M., Franz, C. E., Elman, J. A., Lyons, M. J., Reynolds, C. A., Neale, M. C., Gillespie, N. A., Xian, H., McKenzie, R. E., Toomey, R., Kremen, W. S., Panizzon, M. S., & McEvoy, L. K. (2023). Alcohol use and cognitive aging in middleaged men: The Vietnam Era Twin Study of Aging. *Journal of the International Neuropsychological Society, 29*(3), Article 3. https://doi.org/10.1017/S1355617722000169

54. Enstad, F., Pedersen, W., & von Soest, T. (2023). Adolescent and Young Adult Drunkenness and Future Educational Attainment and Labor Market Integration: A Population-Based Longitudinal Study. *Journal of Studies on Alcohol and Drugs, 84*(1), Article 1. https://doi.org/10.15288/jsad.21-00395

55. Zhou, T., Sun, D., Li, X., Ma, H., Heianza, Y., & Qi, L. (2021). Educational attainment and drinking behaviors: Mendelian randomization study in UK Biobank. *Molecular Psychiatry, 26*(8), Article 8. https://doi.org/10.1038/s41380-019-0596-9

56. Brennan, S. E., McDonald, S., Page, M. J., Reid, J., Ward, S., Forbes, A. B., & McKenzie, J. E. (2020). Long-term effects of alcohol consumption on cognitive function: A systematic review and dose-response analysis of evidence published between 2007 and 2018. *Systematic Reviews, 9*(1), 33. https://doi.org/10.1186/s13643-019-1220-4

57. Hingson, R. W., Heeren, T., & Winter, M. R. (2006). Age of alcohol-dependence onset: Associations with severity of dependence and seeking treatment. *Pediatrics, 118*(3), e755-763. https://doi.org/10.1542/peds.2006-0223

58. Lewis, M. (2019). Brain Change in Addiction as Learning, Not Disease. *The New England Journal of Medicine, 380*(3), 301–302. https://doi.org/10.1056/NEJMc1815144

59. West, R., & Brown, J. (2014). *Theory of addiction* (2nd edition). Wiley Blackwell/Addiction Press.

60. Abbott, C. W., Rohac, D. J., Bottom, R. T., Patadia, S., & Huffman, K. J. (2018). Prenatal Ethanol Exposure and Neocortical Development: A Transgenerational Model of FASD. *Cerebral Cortex, 28*(8), 2908–2921. https://doi.org/10.1093/cercor/bhx168

61. Akison, L. K., Moritz, K. M., & Reid, N. (2019). Adverse reproductive outcomes associated with fetal alcohol exposure: A systematic review. *Reproduction, 157*(4), 329–343. https://doi.org/10.1530/REP-18-0607

62. Ramlau-Hansen, C. H., Toft, G., Jensen, M. S., Strandberg-Larsen, K., Hansen, M. L., & Olsen, J. (2010). Maternal alcohol consumption during pregnancy and semen quality in the male offspring: Two decades of follow-up. *Human Reproduction (Oxford, England), 25*(9), Article 9. https://doi.org/10.1093/humrep/deq140

63. VandeVoort, C. A., Grimsrud, K. N., Midic, U., Mtango, N., & Latham, K. E. (2015). Transgenerational effects of binge drinking in a primate model: Implications for human health. *Fertility and Sterility, 103*(2), Article 2. https://doi.org/10.1016/j.fertnstert.2014.10.051

64. Behnke, M., Smith, V. C., Committee on Substance Abuse, & Committee on Fetus and Newborn. (2013). Prenatal substance abuse: Short- and long-term effects on the exposed fetus. *Pediatrics, 131*(3), Article 3. https://doi.org/10.1542/peds.2012-3931

65. Heller, M., & Burd, L. (2014). Review of ethanol dispersion, distribution, and elimination from the fetal compartment. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 100*(4), Article 4. https://doi.org/10.1002/bdra.23232

66. Fox, D. J., Pettygrove, S., Cunniff, C., O'Leary, L. A., Gilboa, S. M., Bertrand, J., Druschel, C. M., Breen, A., Robinson, L., Ortiz, L., Frías, J. L., Ruttenber, M., Klumb, D., Meaney, F. J., & Centers for Disease Control and Prevention (CDC). (2015). Fetal alcohol syndrome among children aged 7-9 years—Arizona, Colorado, and New York, 2010. *MMWR. Morbidity and Mortality Weekly Report, 64*(3), 54–57.

67. Miller, L., Tolliver, R., Druschel, C., Fox, D., Schoellhorn, J., Podvin, D., Merrick, S., Cuniff, C., Meany, F., Pensak, M., Dominique, Y., Hymbaugh, K., Boyle, C., Baio, J., & Centers for Disease Control and Prevention (CDC). (2002). Fetal Alcohol Syndrome—Alaska, Arizona, Colorado, and New York, 1995–1997. MMWR. *Morbidity and Mortality Weekly Report, 51*(20), 429–452.

68. May, P. A., Baete, A., Russo, J., Elliott, A. J., Blankenship, J., Kalberg, W. O., Buckley, D., Brooks, M., Hasken, J., Abdul-Rahman, O., Adam, M. P., Robinson, L. K., Manning, M., & Hoyme, H. E. (2014). Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics, 134*(5), 855–866. https://doi.org/10.1542/peds.2013-3319

69. May, P. A., Chambers, C. D., Kalberg, W. O., Zellner, J., Feldman, H., Buckley, D., Kopald, D., Hasken, J. M., Xu, R., Honerkamp-Smith, G., Taras, H., Manning, M. A., Robinson, L. K., Adam, M. P., Abdul-Rahman, O., Vaux, K., Jewett, T., Elliott, A. J., Kable, J. A., … Hoyme, H. E. (2018). Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities. *JAMA, 319*(5), 474. https://doi.org/10.1001/jama.2017.21896

70. Lange, S., Probst, C., Gmel, G., Rehm, J., Burd, L., & Popova, S. (2017). Global Prevalence of Fetal Alcohol Spectrum Disorder Among Children and Youth: A Systematic Review and Meta-analysis. *JAMA Pediatrics, 171*(10), 948–956. https://doi.org/10.1001/jamapediatrics.2017.1919

71. Popova, S., Lange, S., Probst, C., Gmel, G., & Rehm, J. (2018). Global prevalence of alcohol use and binge drinking during pregnancy, and fetal alcohol spectrum disorder. *Biochemistry and Cell Biology, 96*(2), 237–240. https://doi.org/10.1139/bcb-2017-0077

72. Sampson, P. D., Streissguth, A. P., Bookstein, F. L., Little, R. E., Clarren, S. K., Dehaene, P., Hanson, J. W., & Graham, J. M. (1997). Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology, 56*(5), 317–326. https://doi.org/10.1002/(SICI)1096-9926(199711)56:5<317::AID-TERA5>3.0.CO;2-U

73. Stratton, K., Howe, C., & Battaglia, F. C. (Eds.). (1996). *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment* (p. 4991). National Academies Press. https://doi.org/10.17226/4991

74. Lupton, C., Burd, L., & Harwood, R. (2004). Cost of fetal alcohol spectrum disorders. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 127C*(1), 42–50. https://doi.org/10.1002/ajmg.c.30015

75. Popova, S., Lange, S., Burd, L., & Rehm, J. (2016). The Economic Burden of Fetal Alcohol Spectrum Disorder in Canada in 2013. *Alcohol and Alcoholism (Oxford, Oxfordshire), 51*(3), 367–375. https://doi.org/10.1093/alcalc/agv117

76. Ericson, L., Magnusson, L., & Hovstadius, B. (2017). Societal costs of fetal alcohol syndrome in Sweden. *The European Journal of Health Economics: HEPAC: Health Economics in Prevention and Care, 18*(5), 575–585. https://doi.org/10.1007/s10198-016-0811-4

77. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2020). *Alcohol, pregnancy and infant health – a shared responsibility* (Alcohol and Society).

78. Flak, A. L., Su, S., Bertrand, J., Denny, C. H., Kesmodel, U. S., & Cogswell, M. E. (2014). The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: A meta-analysis. *Alcoholism, Clinical and Experimental Research, 38*(1), Article 1. https://doi.org/10.1111/acer.12214

79. Nunez, C. C., Roussotte, F., & Sowell, E. R. (2011). Focus on: Structural and functional brain abnormalities in fetal alcohol spectrum disorders. *Alcohol Research & Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism, 34*(1), Article 1.

80. Jones, K. L. (2011). The effects of alcohol on fetal development. *Birth Defects Research Part C: Embryo Today: Reviews, 93*(1), 3–11. https://doi.org/10.1002/bdrc.20200

81. Kingdon, D., Cardoso, C., & McGrath, J. J. (2016). Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder – a meta-analysis. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 57*(2), 116–131. https://doi.org/10.1111/jcpp.12451

82. Mattson, S. N., Crocker, N., & Nguyen, T. T. (2011). Fetal alcohol spectrum disorders: Neuropsychological and behavioral features. *Neuropsychology Review, 21*(2), 81–101. https://doi.org/10.1007/s11065-011-9167-9

83. Mattson, S. N., Bernes, G. A., & Doyle, L. R. (2019). Fetal Alcohol Spectrum Disorders: A Review of the Neurobehavioral Deficits Associated With Prenatal Alcohol Exposure. *Alcoholism: Clinical and Experimental Research, 43*(6), 1046–1062. https://doi.org/10.1111/acer.14040

84. Mattson, S. N., & Riley, E. P. (1998). A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism, Clinical and Experimental Research, 22*(2), 279–294. https://doi.org/10.1111/j.1530-0277.1998.tb03651.x

85. Mattson, S. N., & Riley, E. P. (1999). Implicit and explicit memory functioning in children with heavy prenatal alcohol exposure. *Journal of the International Neuropsychological Society: JINS, 5*(5), 462–471. https://doi.org/10.1017/s1355617799555082

86. Streissguth, A. P., Barr, H., Kogan, J., & Bookstein, F. L. (1996). *Understanding the Occurrence of Secondary Disabilities in Clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE). Final Report to the Centers for Disease Control and Prevention (CDC).* (96–06; Technical Report). University of Washington.

87. Ferreira, V. K. de L., & Cruz, M. S. (2017). Intelligence and Fetal Alcohol Spectrum Disorders: A Review. *Journal of Population Therapeutics and Clinical Pharmacology = Journal De La Therapeutique Des Populations Et De La Pharmacologie Clinique, 24*(3), e1–e18. https://doi.org/10.22374/1710-6222.24.3.1

88. Mattson, S. N., Riley, E. P., Gramling, L., Delis, D. C., & Jones, K. L. (1997). Heavy pre-natal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *The Journal of Pediatrics, 131*(5), 718–721. https://doi.org/10.1016/s0022-3476(97)70099-4

89. Connor, P. D., Sampson, P. D., Streissguth, A. P., Bookstein, F. L., & Barr, H. M. (2006). Effects of prenatal alcohol exposure on fine motor coordination and balance: A study of two adult samples. *Neuropsychologia, 44*(5), 744–751. https://doi.org/10.1016/j.neuropsychologia.2005.07.016

90. Doney, R., Lucas, B. R., Jones, T., Howat, P., Sauer, K., & Elliott, E. J. (2014). Fine motor skills in children with prenatal alcohol exposure or fetal alcohol spectrum disorder. *Journal of Developmental and Behavioral Pediatrics: JDBP, 35*(9), 598–609. https://doi.org/10.1097/DBP.0000000000000107

91. Adnams, C. M., Kodituwakku, P. W., Hay, A., Molteno, C. D., Viljoen, D., & May, P. A. (2001). Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcoholism, Clinical and Experimental Research, 25*(4), 557–562.

92. Kalberg, W. O., Provost, B., Tollison, S. J., Tabachnick, B. G., Robinson, L. K., Eugene Hoyme, H., Trujillo, P. M., Buckley, D., Aragon, A. S., & May, P. A. (2006). Comparison of motor delays in young children with fetal alcohol syndrome to those with prenatal alcohol exposure and with no prenatal alcohol exposure. *Alcoholism, Clinical and Experimental Research, 30*(12), 2037–2045. https://doi.org/10.1111/j.1530-0277.2006.00250.x

93. Lucas, B. R., Latimer, J., Pinto, R. Z., Ferreira, M. L., Doney, R., Lau, M., Jones, T., Dries, D., & Elliott, E. J. (2014). Gross motor deficits in children prenatally exposed to alcohol: A meta-analysis. *Pediatrics, 134*(1), e192-209. https://doi.org/10.1542/peds.2013-3733

94. Bertrand, J., Floyd, L. L., Weber, M. K., & Fetal Alcohol Syndrome Prevention Team, Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC). (2005). Guidelines for identifying and referring persons with fetal alcohol syndrome. *MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report. Recommendations and Reports, 54*(RR-11), 1–14.

95. Kodituwakku, P. W., Handmaker, N. S., Cutler, S. K., Weathersby, E. K., & Handmaker, S. D. (1995). Specific impairments in self-regulation in children exposed to alcohol prenatally. *Alcoholism, Clinical and Experimental Research, 19*(6), 1558–1564. https://doi.org/10.1111/j.1530-0277.1995.tb01024.x

96. Nanson, J. L., & Hiscock, M. (1990). Attention deficits in children exposed to alcohol prenatally. *Alcoholism, Clinical and Experimental Research, 14*(5), 656–661. https://doi.org/10.1111/j.1530-0277.1990.tb01223.x

97. Streissguth, A. P., Sampson, P. D., Olson, H. C., Bookstein, F. L., Barr, H. M., Scott, M., Feldman, J., & Mirsky, A. F. (1994). Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring--a longitudinal prospective study. *Alcoholism, Clinical and Experimental Research, 18*(1), 202–218. https://doi.org/10.1111/j.1530-0277.1994.tb00904.x

98. Coles, C. D., Platzman, K. A., Lynch, M. E., & Freides, D. (2002). Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. *Alcoholism, Clinical and Experimental Research, 26*(2), 263–271.

99. Connor, P. D., Streissguth, A. P., Sampson, P. D., Bookstein, F. L., & Barr, H. M. (1999). Individual differences in auditory and visual attention among fetal alcohol-affected adults. *Alcoholism, Clinical and Experimental Research, 23*(8), 1395–1402.

100. Mattson, S. N., Calarco, K. E., & Lang, A. R. (2006). Focused and shifting attention in children with heavy prenatal alcohol exposure. *Neuropsychology, 20*(3), 361–369. https://doi.org/10.1037/0894-4105.20.3.361

101. Rasmussen, C., Tamana, S., Baugh, L., Andrew, G., Tough, S., & Zwaigenbaum, L. (2013). Neuropsychological impairments on the NEPSY-II among children with FASD. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence, 19*(4), 337–349. https://doi.org/10.1080/09297049.2012.658768

102. Lee, K. T., Mattson, S. N., & Riley, E. P. (2004). Classifying children with heavy prenatal alcohol exposure using measures of attention. *Journal of the International Neuropsychological Society: JINS,* 10(2), 271–277. https://doi.org/10.1017/S1355617704102142

103. Wozniak, J. R., Riley, E. P., & Charness, M. E. (2019). Clinical presentation, diagnosis, and management of fetal alcohol spectrum disorder. *The Lancet. Neurology, 18*(8), 760–770. https://doi.org/10.1016/S1474-4422(19)30150-4

104. Abate, P., Pueta, M., Spear, N. E., & Molina, J. C. (2008). Fetal Learning About Ethanol and Later Ethanol Responsiveness: Evidence Against "Safe" Amounts of Prenatal Exposure. *Experimental Biology and Medicine, 233*(2), 139–154. https://doi.org/10.3181/0703-MR-69

105. Comasco, E., Rangmar, J., Eriksson, U. J., & Oreland, L. (2018). Neurological and neuropsychological effects of low and moderate prenatal alcohol exposure. *Acta Physiologica (Oxford, England), 222*(1), Article 1. https://doi.org/10.1111/apha.12892

106. *GBD Compare Data Visualization*. (2020). Institute for Health Metrics and Evaluation (IHME), Seattle, WA: IHME, University of Washington, 2020. http://vizhub.healthdata.org/gbd-compare

107. Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences, 1021*, 77–85. https://doi.org/10.1196/annals.1308.009

108. Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 8174–8179. https://doi.org/10.1073/pnas.0402680101

109. Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews, 30*(6), 718–729. https://doi.org/10.1016/j.neubiorev.2006.06.001

110. Reiss, A. L., Abrams, M. T., Singer, H. S., Ross, J. L., & Denckla, M. B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain: A Journal of Neurology, 119* (Pt 5), 1763–1774. https://doi.org/10.1093/brain/119.5.1763

111. Tapert, S. (2022). Alcohol and the Adolescent Brain: What We've Learned and Where the Data Are Taking Us. *Alcohol Research: Current Reviews, 42*(1), Article 1. https://doi.org/10.35946/arcr.v42.1.07

112. Sicher, A. R., Duerr, A., Starnes, W. D., & Crowley, N. A. (2022). Adolescent Alcohol and Stress Exposure Rewires Key Cortical Neurocircuitry. *Frontiers in Neuroscience, 16*, 896880. https://doi.org/10.3389/fnins.2022.896880

113. Bellis, M. D., Narasimhan, A., Thatcher, D. L., Keshavan, M. S., Soloff, P., & Clark, D. B. (2005). Prefrontal Cortex, Thalamus, and Cerebellar Volumes in Adolescents and Young Adults with Adolescent-Onset Alcohol Use Disorders and Comorbid Mental Disorders. *Alcoholism: Clinical and Experimental Research, 29*(9), 1590–1600. https://doi.org/10.1097/01.alc.0000179368.87886.76

114. Medina, K. L., McQueeny, T., Nagel, B. J., Hanson, K. L., Schweinsburg, A. D., & Tapert, S. F. (2008). Prefrontal cortex volumes in adolescents with alcohol use disorders: Unique gender effects. *Alcoholism, Clinical and Experimental Research, 32*(3), 386–394. https://doi.org/10.1111/j.1530-0277.2007.00602.x

115. Jones, S. A., & Nagel, B. J. (2019). Altered frontostriatal white matter microstructure is associated with familial alcoholism and future binge drinking in adolescence. *Neuropsychopharmacology, 44*(6), 1076–1083. https://doi.org/10.1038/s41386-019-0315-x

116. Bedi, A., McGlinchey, R. E., Salat, D. H., Currao, A., Fonda, J. R., Milberg, W. P., & Fortier, C. B. (2021). Age of onset of adolescent binge drinking is differentially associated with cortical thickness in post-9/11 adult Veterans. *Alcoholism, Clinical and Experimental Research, 45*(5), 1065–1077. https://doi.org/10.1111/acer.14606

117. Duncan, S. C., Alpert, A., Duncan, T. E., & Hops, H. (1997). Adolescent alcohol use development and young adult outcomes. *Drug and Alcohol Dependence, 49*(1), 39–48. https://doi.org/10.1016/S0376-8716(97)00137-3

118. Enstad, F., Evans-Whipp, T., Kjeldsen, A., Toumbourou, J. W., & Von Soest, T. (2019). Predicting hazardous drinking in late adolescence/young adulthood from early and excessive adolescent drinking—A longitudinal cross-national study of Norwegian and Australian adolescents. *BMC Public Health, 19*(1), 790. https://doi.org/10.1186/s12889-019-7099-0

119. Magee, K. E., & Connell, A. M. (2021). The role of substance use coping in linking depression and alcohol use from late adolescence through early adulthood. *Experimental and Clinical Psychopharmacology, 29*(6), 659–669. https://doi.org/10.1037/pha0000436

120. Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J. O., Aravkin, A. Y., Bang-Jensen, B. L., Bertolacci, G. J., Bloom, S. S., Castellano, R., Castro, E., Chakrabarti, S., Chattopadhyay, J., Cogen, R. M., Collins, J. K., … Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet, 398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7

121. WHO. (2023). *Depression*. https://www.who.int/health-topics/depression

122. WHO. (2023, March 31). *Depressive disorder (depression)*. https://www.who.int/news-room/fact-sheets/detail/depression

123. Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Scientific Reports, 8*(1), 2861. https://doi.org/10.1038/s41598-018-21243-x

124. WHO. (2014). *Preventing suicide: A global imperative*. World Health Organization. https://iris.who.int/handle/10665/131056

125. WHO. (2023, August 28). *Suicide*. https://www.who.int/news-room/fact-sheets/detail/suicide

126. WHO. (2021, February 9). *GHO | By category | Suicide rate estimates, age-standardized – Estimates by country*. WHO; World Health Organization. https://apps.who.int/gho/data/view.main.MHSUICIDEASDRv?lang=en

127. Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2009). Tests of causal links between alcohol abuse or dependence and major depression. *Archives of General Psychiatry, 66*(3), 260–266. https://doi.org/10.1001/archgenpsychiatry.2008.543

128. Puddephatt, J., Irizar, P., Jones, A., Gage, S. H., & Goodwin, L. (2022). Associations of common mental disorder with alcohol use in the adult general population: A systematic review and meta-analysis. *Addiction, 117*(6), Article 6. https://doi.org/10.1111/add.15735

129. Li, J., Wang, H., Li, M., Shen, Q., Li, X., Zhang, Y., Peng, J., Rong, X., & Peng, Y. (2020). Effect of alcohol use disorders and alcohol intake on the risk of subsequent depressive symptoms: A systematic review and meta-analysis of cohort studies. *Addiction, 115*(7), Article 7. https://doi.org/10.1111/add.14935

130. Hammerton, G., Lewis, G., Heron, J., Fernandes, G., Hickman, M., & Lewis, G. (2023). The association of alcohol dependence and consumption during adolescence with depression in young adulthood, in England: A prospective cohort study. *The Lancet Psychiatry, 10*(7), Article 7. https://doi.org/10.1016/S2215-0366(23)00138-4

131. Rehm, J., Marmet, S., Anderson, P., Gual, A., Kraus, L., Nutt, D. J., Room, R., Samokhvalov, A. V., Scafato, E., Trapencieris, M., Wiers, R. W., & Gmel, G. (2013). Defining Substance Use Disorders: Do We Really Need More Than Heavy Use? *Alcohol and Alcoholism, 48*(6), 633–640. https://doi.org/10.1093/alcalc/agt127

132. Peter, L.-J., Rocío, G.-J., Miquel, R., Margalida, G., Adoración, C., María Ángeles, P.-A., Joan, S., Pau, R., & Mauro, G.-T. (2022). Moderate alcohol consumption and depression prevention: A critical review. *Actas Espanolas De Psiquiatria, 50*(3), Article 3.

133. Visontay, R., Mewton, L., Slade, T., Aris, I. M., & Sunderland, M. (2023). Moderate Alcohol Consumption and Depression: A Marginal Structural Model Approach Promoting Causal Inference. *American Journal of Psychiatry, 180*(3), Article 3. https://doi.org/10.1176/appi.ajp.22010043

134. Xu, Y., Zeng, L., Zou, K., Shan, S., Wang, X., Xiong, J., Zhao, L., Zhang, L., & Cheng, G. (2021). Role of dietary factors in the prevention and treatment for depression: An umbrella review of meta-analyses of prospective studies. *Translational Psychiatry, 11*(1), Article 1. https://doi.org/10.1038/s41398-021-01590-6

135. Gémes, K., Forsell, Y., Janszky, I., László, K. D., Lundin, A., Ponce De Leon, A., Mukamal, K. J., & Moller, J. (2019). Moderate alcohol consumption and depression – a longitudinal population-based study in Sweden. *Acta Psychiatrica Scandinavica, 139*(6), Article 6. https://doi.org/10.1111/acps.13034

136. Fredman Stein, K., Allen, J. L., Robinson, R., Smith, C., Sawyer, K., & Taylor, G. (2022). Do interventions principally targeting excessive alcohol use in young people improve depression symptoms?: A systematic review and meta-analysis. *BMC Psychiatry, 22*(1), Article 1. https://doi.org/10.1186/s12888-022-04006-x

137. de Boer, N., Vermeulen, J., Lin, B., van Os, J., ten Have, M., de Graaf, R., van Dorsselaer, S., Bak, M., Rutten, B., Batalla, A., Guloksuz, S., & Luykx, J. J. (2023). Longitudinal associations between alcohol use, smoking, genetic risk scoring and symptoms of depression in the general population: A prospective 6-year cohort study. *Psychological Medicine, 53*(4), Article 4. https://doi.org/10.1017/S0033291721002968

138. Sallis, H. M., Palmer, T., Tilling, K., Davey Smith, G., & Munafò, M. R. (2023). Using allele scores to identify confounding by reverse causation: Studies of alcohol consumption as an exemplar. *International Journal of Epidemiology, 52*(2), Article 2. https://doi.org/10.1093/ije/dyac165

139. Borges, G., Bagge, C. L., Cherpitel, C. J., Conner, K. R., Orozco, R., & Rossow, I. (2017). A meta-analysis of acute use of alcohol and the risk of suicide attempt. *Psychological Medicine, 47*(5), 949–957. https://doi.org/10.1017/S0033291716002841

140. Darvishi, N., Farhadi, M., Haghtalab, T., & Poorolajal, J. (2015). Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: A meta-analysis. *PloS One, 10*(5), e0126870. https://doi.org/10.1371/journal.pone.0126870

141. Isaacs, J. Y., Smith, M. M., Sherry, S. B., Seno, M., Moore, M. L., & Stewart, S. H. (2022). Alcohol use and death by suicide: A meta-analysis of 33 studies. *Suicide and Life-Threatening Behavior, 52*(4), Article 4. https://doi.org/10.1111/sltb.12846

142. Kaplan, M. S., McFarland, B. H., Huguet, N., Conner, K., Caetano, R., Giesbrecht, N., & Nolte, K. B. (2013). Acute alcohol intoxication and suicide: A gender-stratified analysis of the National Violent Death Reporting System. *Injury Prevention: Journal of the International Society for Child and Adolescent Injury Prevention, 19*(1), 38–43. https://doi.org/10.1136/injuryprev-2012-040317

143. Lange, S., Jiang, H., Kaplan, M. S., Kim, K. V., & Rehm, J. (2023). Association Between Acute Alcohol Use and Firearm-Involved Suicide in the United States. *JAMA Network Open, 6*(3), e235248. https://doi.org/10.1001/jamanetworkopen.2023.5248

144. Norström, T., & Ramstedt, M. (2018). The Link Between Per Capita Alcohol Consumption and Alcohol-Related Harm in Sweden, 1987-2015. *Journal of Studies on Alcohol and Drugs, 79*(4), Article 4.

145. Kerr, W. C., Subbaraman, M., & Ye, Y. (2011). Per capita alcohol consumption and suicide mortality in a panel of US states from 1950 to 2002: Alcohol and suicide mortality in the USA. *Drug and Alcohol Review, 30*(5), Article 5. https://doi.org/10.1111/j.1465-3362.2011.00306.x

146. O'Connor, M. J., Portnoff, L. C., Lebsack-Coleman, M., & Dipple, K. M. (2019). Suicide risk in adolescents with fetal alcohol spectrum disorders. *Birth Defects Research, 111*(12), 822–828. https://doi.org/10.1002/bdr2.1465

147. Kõlves, K., Chitty, K. M., Wardhani, R., Värnik, A., de Leo, D., & Witt, K. (2020). Impact of Alcohol Policies on Suicidal Behavior: A Systematic Literature Review. *International Journal of Environmental Research and Public Health, 17*(19), Article 19. https://doi.org/10.3390/ijerph17197030

148. Xuan, Z., Naimi, T. S., Kaplan, M. S., Bagge, C. L., Few, L. R., Maisto, S., Saitz, R., & Freeman, R. (2016). Alcohol Policies and Suicide: A Review of the Literature. *Alcoholism: Clinical and Experimental Research, 40*(10), Article 10. https://doi.org/10.1111/acer.13203

149. Breslow, R. A., Castle, I.-J. P., Chen, C. M., & Graubard, B. I. (2017). Trends in Alcohol Consumption Among Older Americans: National Health Interview Surveys, 1997 to 2014. *Alcoholism, Clinical and Experimental Research, 41*(5), 976–986. https://doi.org/10.1111/acer.13365

150. Calvo, E., Medina, J. T., Ornstein, K. A., Staudinger, U. M., Fried, L. P., & Keyes, K. M. (2020). Cross-country and historical variation in alcohol consumption among older men and women: Leveraging recently harmonized survey data in 21 countries. *Drug and Alcohol Dependence, 215*, 108219. https://doi.org/10.1016/j.drugalcdep.2020.108219

151. Guttormsson, U. (2022). *Alkoholvanor hos äldre 2004–2021 (Alchohol consumption of older people 2004–2021)* (p. 16). Centralförbundet för alkohol- och narkotikaupplysning. https://www.can.se/app/uploads/2022/11/alkoholvanor-hos-aldre-2004-2021.pdf

152. Han, B. H., Moore, A. A., Sherman, S., Keyes, K. M., & Palamar, J. J. (2017). Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005-2014. *Drug and Alcohol Dependence, 170,* 198–207. https://doi.org/10.1016/j.drugalcdep.2016.11.003

153. Livingston, M., Callinan, S., Dietze, P., Stanesby, O., & Kuntsche, E. (2018). Is there gender convergence in risky drinking when taking birth cohorts into account? Evidence from an Australian national survey 2001-13. *Addiction (Abingdon, England), 113*(11), 2019–2028. https://doi.org/10.1111/add.14279

154. GBD 2016 Dementia Collaborators. (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology, 18*(1), 88–106. https://doi.org/10.1016/S1474-4422(18)30403-4

155. GBD 2019 Dementia Forecasting Collaborators. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *The Lancet. Public Health, 7*(2), e105–e125. https://doi.org/10.1016/S2468-2667(21)00249-8

156. WHO. (2019). *Risk reduction of cognitive decline and dementia: WHO guidelines.* World Health Organization. https://iris.who.int/handle/10665/312180

157. Wimo, A., Seeher, K., Cataldi, R., Cyhlarova, E., Dielemann, J. L., Frisell, O., Guerchet, M., Jönsson, L., Malaha, A. K., Nichols, E., Pedroza, P., Prince, M., Knapp, M., & Dua, T. (2023). The worldwide costs of dementia in 2019. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 19*(7), 2865–2873. https://doi.org/10.1002/alz.12901

158. Wimo, A., Jönsson, L., Fratiglioni, L., Sandman, P. O., Gustavsson, A., Sköldunger, A., & Johansson, L. (2016). The societal costs of dementia in Sweden 2012 – Relevance and methodological challenges in valuing informal care. *Alzheimer's Research & Therapy, 8*(1), 59. https://doi.org/10.1186/s13195-016-0215-9

159. WHO. (2017). *Global action plan on the public health response to dementia 2017–2025.* World Health Organization. https://iris.who.int/handle/10665/259615

160. Andréasson, S., Chikritzhs, T., Dangardt, F., Holder, H., Naimi, T., & Stockwell, T. (2023). *Alcohol and blood pressure* (Alcohol and Society). CERA, SFAM, Swedish Society of Nursing, SAFF, Movendi International, Riksförbundet HjärtLung, SLAN, Swedish society of addiction medicine, SIGHT, IOGT-NTO.

161. Chandrakumar, A., Bhardwaj, A., & 'T Jong, G. W. (2019). Review of thiamine deficiency disorders: Wernicke encephalopathy and Korsakoff psychosis. *Journal of Basic and Clinical Physiology and Pharmacology, 30*(2), 153–162. https://doi.org/10.1515/jbcpp-2018-0075

162. 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

163. Schwarzinger, M., Pollock, B. G., Hasan, O. S. M., Dufouil, C., Rehm, J., & QalyDays Study Group. (2018). Contribution of alcohol use disorders to the burden of dementia in France 2008-13: A nationwide retrospective cohort study. *The Lancet. Public Health, 3*(3), Article 3. https://doi.org/10.1016/S2468-2667(18)30022-7

164. Mewton, L., Visontay, R., Hoy, N., Lipnicki, D. M., Sunderland, M., Lipton, R. B., Guerchet, M., Ritchie, K., Najar, J., Scarmeas, N., Kim, K., Riedel Heller, S., van Boxtel, M., Jacobsen, E., Brodaty, H., Anstey, K. J., Haan, M., Scazufca, M., Lobo, E., … Collaborators from the Cohort Studies of Memory in an International Consortium (COSMIC). (2023). 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), Article 3. https://doi.org/10.1111/add.16035

165. Bosi, M., Malavolti, M., Garuti, C., Tondelli, M., Marchesi, C., Vinceti, M., & Filippini, T. (2022). Environmental and lifestyle risk factors for early-onset dementia: A systematic review: Environmental factors and EOD risk. *Acta Biomedica Atenei Parmensis, 93*(6), Article 6. https://doi.org/10.23750/abm.v93i6.13279

166. 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 1. https://doi.org/10.1186/s12877-023-03972-5

167. Lao, Y., Hou, L., Li, J., Hui, X., Yan, P., & Yang, K. (2021). Association between alcohol intake, mild cognitive impairment and progression to dementia: A dose-response meta-analysis. *Aging Clinical and Experimental Research, 33*(5), Article 5. https://doi.org/10.1007/s40520-020-01605-0

168. Wiegmann, C., Mick, I., Brandl, E. J., Heinz, A., & Gutwinski, S. (2020). Alcohol and Dementia – What is the Link? A Systematic Review. *Neuropsychiatric Disease and Treatment, 16*, 87–99. https://doi.org/10.2147/NDT.S198772

169. Xie, C., & Feng, Y. (2022). Alcohol consumption and risk of Alzheimer's disease: A dose-response meta-analysis. *Geriatrics & Gerontology International, 22*(4), Article 4. https://doi.org/10.1111/ggi.14357

170. Xu, W., Wang, H., Wan, Y., Tan, C., Li, J., Tan, L., & Yu, J.-T. (2017). Alcohol consumption and dementia risk: A dose-response meta-analysis of prospective studies. *European Journal of Epidemiology, 32*(1), 31–42. https://doi.org/10.1007/s10654-017-0225-3

171. Westman, J., Wahlbeck, K., Laursen, T. M., Gissler, M., Nordentoft, M., Hällgren, J., Arffman, M., & Ösby, U. (2015). Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. *Acta Psychiatrica Scandinavica, 131*(4), 297–306. https://doi.org/10.1111/acps.12330

172. Mukamal, K. J. (2003). Prospective Study of Alcohol Consumption and Risk of Dementia in Older Adults. *JAMA, 289*(11), 1405. https://doi.org/10.1001/jama.289.11.1405

173. Ganguli, M., Bilt, J. V., Saxton, J. A., Shen, C., & Dodge, H. H. (2005). Alcohol consumption and cognitive function in late life: A longitudinal community study. *Neurology, 65*(8), 1210–1217. https://doi.org/10.1212/01.wnl.0000180520.35181.24

174. Naimi, T. S., Stadtmueller, L. A., Chikritzhs, T., Stockwell, T., Zhao, J., Britton, A., Saitz, R., & Sherk, A. (2019). Alcohol, Age, and Mortality: Estimating Selection Bias Due to Premature Death. *Journal of Studies on Alcohol and Drugs, 80*(1), Article 1.

175. Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2014). Alcohol consumption and cognitive impairment in older men: A mendelian randomization study. *Neurology, 82*(12), 1038–1044. https://doi.org/10.1212/WNL.0000000000000255

176. Andrews, S. J., Goate, A., & Anstey, K. J. (2020). Association between alcohol consumption and Alzheimer's disease: A Mendelian randomization study. *Alzheimer's & Dementia, 16*(2), Article 2. https://doi.org/10.1016/j.jalz.2019.09.086

177. Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ*, j5375. https://doi.org/10.1136/bmj.j5375

178. Verbaten, M. N. (2009). Chronic effects of low to moderate alcohol consumption on structural and functional properties of the brain: Beneficial or not? *Human Psycho-pharmacology, 24*(3), Article 3. https://doi.org/10.1002/hup.1022

179. Day, S. M., Gironda, S. C., Clarke, C. W., Snipes, J. A., Nicol, N. I., Kamran, H., Vaughan, W., Weiner, J. L., & Macauley, S. L. (2023). Ethanol exposure alters Alzheimer's-related pathology, behavior, and metabolism in APP/PS1 mice. *Neurobiology of Disease, 177,* 105967. https://doi.org/10.1016/j.nbd.2022.105967

180. Hoffman, J. L., Faccidomo, S., Kim, M., Taylor, S. M., Agoglia, A. E., May, A. M., Smith, E. N., Wong, L. C., & Hodge, C. W. (2019). Alcohol drinking exacerbates neural and behavioral pathology in the 3xTg-AD mouse model of Alzheimer's disease. *International Review of Neurobiology, 148*, 169–230. https://doi.org/10.1016/bs.irn.2019.10.017

181. Huang, D., Yu, M., Yang, S., Lou, D., Zhou, W., Zheng, L., Wang, Z., Cai, F., Zhou, W., Li, T., & Song, W. (2018). Ethanol Alters APP Processing and Aggravates Alzheimer-Associated Phenotypes. *Molecular Neurobiology, 55*(6), 5006–5018. https://doi.org/10.1007/s12035-017-0703-3

182. Deuschl, G., Beghi, E., Fazekas, F., Varga, T., Christoforidi, K. A., Sipido, E., Bassetti, C. L., Vos, T., & Feigin, V. L. (2020). The burden of neurological diseases in Europe: An analysis for the Global Burden of Disease Study 2017. *The Lancet. Public Health, 5*(10), e551–e567. https://doi.org/10.1016/S2468-2667(20)30190-0

183. GBD 2017 US Neurological Disorders Collaborators, Feigin, V. L., Vos, T., Alahdab, F., Amit, A. M. L., Bärnighausen, T. W., Beghi, E., Beheshti, M., Chavan, P. P., Criqui, M. H., Desai, R., Dhamminda Dharmaratne, S., Dorsey, E. R., Wilder Eagan, A., Elgendy, I. Y., Filip, I., Giampaoli, S., Giussani, G., Hafezi-Nejad, N., … Murray, C. J. L. (2021). Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study. *JAMA Neurology, 78*(2), 165–176. https://doi.org/10.1001/jamaneurol.2020.4152

184. Girotra, T., Lekoubou, A., Bishu, K. G., & Ovbiagele, B. (2020). A contemporary and comprehensive analysis of the costs of stroke in the United States. *Journal of the Neurological Sciences, 410*, 116643. https://doi.org/10.1016/j.jns.2019.116643

185. Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types – A systematic review and meta-analysis. *BMC Public Health, 10*, 258. https://doi.org/10.1186/1471-2458-10-258

186. Rehm, J., Shield, K. D., Roerecke, M., & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: An overview. *BMC Public Health, 16*, 363. https://doi.org/10.1186/s12889-016-3026-9

187. Jones, S. B., Loehr, L., Avery, C. L., Gottesman, R. F., Wruck, L., Shahar, E., & Rosamond, W. D. (2015). Midlife Alcohol Consumption and the Risk of Stroke in the Atherosclerosis Risk in Communities Study. *Stroke, 46*(11), 3124–3130. https://doi.org/10.1161/STROKEAHA.115.010601

188. Wood, A. M., Kaptoge, S., Butterworth, A. S., Willeit, P., Warnakula, S., Bolton, T., Paige, E., Paul, D. S., Sweeting, M., Burgess, S., Bell, S., Astle, W., Stevens, D., Koulman, A., Selmer, R. M., Verschuren, W. M. M., Sato, S., Njølstad, I., Woodward, M., … Danesh, J. (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), Article 10129. https://doi.org/10.1016/S0140-6736(18)30134-X

189. Holmes, M. V., Dale, C. E., Zuccolo, L., Silverwood, R. J., Guo, Y., Ye, Z., Prieto-Merino, D., Dehghan, A., Trompet, S., Wong, A., Cavadino, A., Drogan, D., Padmanabhan, S., Li, S., Yesupriya, A., Leusink, M., Sundstrom, J., Hubacek, J. A., Pikhart, H., … on behalf of The InterAct Consortium. (2014). Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ, 349*(jul10 6), Article jul10 6. https://doi.org/10.1136/bmj.g4164

190. Millwood, I. Y., Walters, R. G., Mei, X. W., Guo, Y., Yang, L., Bian, Z., Bennett, D. A., Chen, Y., Dong, C., Hu, R., Zhou, G., Yu, B., Jia, W., Parish, S., Clarke, R., Davey Smith, G., Collins, R., Holmes, M. V., Li, L., … China Kadoorie Biobank Collaborative Group. (2019). Conventional and genetic evidence on alcohol and vascular disease aetiology: A prospective study of 500 000 men and women in China. *Lancet (London, England), 393*(10183), Article 10183. https://doi.org/10.1016/S0140-6736(18)31772-0

191. GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England), 396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9

192. GBD 2017 Causes of Death Collaborators. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England), 392*(10159), 1736–1788. https://doi.org/10.1016/S0140-6736(18)32203-7

193. Cherpitel, C. J., Witbrodt, J., Ye, Y., & Korcha, R. (2018). A multi-level analysis of emergency department data on drinking patterns, alcohol policy and cause of injury in 28 countries. *Drug and Alcohol Dependence, 192,* 172–178. https://doi.org/10.1016/j.drugalcdep.2018.07.033

194. Wu, H. Z., Barry, L. C., Duan, Y., Bohannon, R. W., Covault, J. M., & Grady, J. J. (2017). Acute Effects of Moderate Alcohol Consumption on Postural Stability in Older Adults. *Perceptual and Motor Skills, 124*(5), Article 5. https://doi.org/10.1177/0031512517721069

195. Stenbacka, M., Jansson, B., Leifman, A., & Romelsjö, A. (2002). Association between use of sedatives or hypnotics, alcohol consumption, or other risk factors and a single injurious fall or multiple injurious falls: A longitudinal general population study. *Alcohol (Fayetteville, N.Y.), 28*(1), 9–16. https://doi.org/10.1016/s0741-8329(02)00223-9

196. Bye, E. K., Bogstrand, S. T., & Rossow, I. (2022). The importance of alcohol in elderly's hospital admissions for fall injuries: A population case-control study. *Nordisk Alkohol- & Narkotikatidskrift: NAT, 39*(1), 38–49. https://doi.org/10.1177/14550725211015836

197. Anderson, P., Scafato, E., Galluzzo, L., & VINTAGE project Working Group. (2012). Alcohol and older people from a public health perspective. *Annali Dell'Istituto Superiore Di Sanita, 48*(3), 232–247. https://doi.org/10.4415/ANN_12_03_04

198. Galluzzo, L., Scafato, E., Martire, S., Anderson, P., Colom, J., Segura, L., McNeill, A., Sovinova, H., Rados Krnel, S., Ahlström, S., & VINTAGE project Working Group. (2012). Alcohol and older people. The European project VINTAGE: Good health into older age. Design, methods and major results. *Annali Dell'Istituto Superiore Di Sanita, 48*(3), 221–231. https://doi.org/10.4415/ANN_12_03_03

199. Hartikainen, S., Lönnroos, E., & Louhivuori, K. (2007). Medication as a risk factor for falls: Critical systematic review. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62*(10), 1172–1181. https://doi.org/10.1093/gerona/62.10.1172

200. Woolcott, J. C., Richardson, K. J., Wiens, M. O., Patel, B., Marin, J., Khan, K. M., & Marra, C. A. (2009). Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine, 169*(21), 1952–1960. https://doi.org/10.1001/archinternmed.2009.357

201. Laurence, B. D., & Michel, L. (2017). The Fall in Older Adults: Physical and Cognitive Problems. *Current Aging Science, 10*(3), 185–200. https://doi.org/10.2174/1874609809666160630124552

202. Lipardo, D. S., Aseron, A. M. C., Kwan, M. M., & Tsang, W. W. (2017). Effect of Exercise and Cognitive Training on Falls and Fall-Related Factors in Older Adults With Mild Cognitive Impairment: A Systematic Review. *Archives of Physical Medicine and Rehabilitation, 98*(10), 2079–2096. https://doi.org/10.1016/j.apmr.2017.04.021

203. Zhang, W., Low, L.-F., Schwenk, M., Mills, N., Gwynn, J. D., & Clemson, L. (2019). Review of Gait, Cognition, and Fall Risks with Implications for Fall Prevention in Older Adults with Dementia. *Dementia and Geriatric Cognitive Disorders, 48*(1–2), 17–29. https://doi.org/10.1159/000504340

204. Zhao, J., Stockwell, T., Vallance, K., & Hobin, E. (2020). The Effects of Alcohol Warning Labels on Population Alcohol Consumption: An Interrupted Time Series Analysis of Alcohol Sales in Yukon, Canada. *Journal of Studies on Alcohol and Drugs, 81*(2), Article 2. https://doi.org/10.15288/jsad.2020.81.225

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