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Alcohol Use Disorder and Dementia: A Review

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PURPOSE: By 2040, 21.6% of Americans will be over age 65, and the population of those older than age 85 is estimated to reach 14.4 million. Although not causative, older age is a risk factor for dementia: every 5 years beyond age 65, the risk doubles; approximately one-third of those older than age 85 are diagnosed with dementia. As current alcohol consumption among older adults is significantly higher compared to previous generations, a pressing question is whether drinking alcohol increases the risk for Alzheimer's disease or other forms of dementia.
SEARCH METHODS: Databases explored included PubMed, Web of Science, and ScienceDirect. To accomplish this narrative review on the effects of alcohol consumption on dementia risk, the literature covered included clinical diagnoses, epidemiology, neuropsychology, postmortem pathology, neuroimaging and other biomarkers, and translational studies. Searches conducted between January 12 and August 1, 2023, included the following terms and combinations: "aging," "alcoholism," "alcohol use disorder (AUD)," "brain," "CNS," "dementia," "Wernicke," "Korsakoff," "Alzheimer," "vascular," "frontotemporal," "Lewy body," "clinical," "diagnosis," "epidemiology," "pathology," "autopsy," "postmortem," "histology," "cognitive," "motor," "neuropsychological," "magnetic resonance," "imaging," "PET," "ligand," "degeneration," "atrophy," "translational," "rodent," "rat," "mouse," "model," "amyloid," "neurofibrillary tangles," "α-synuclein," or "presenilin." When relevant, "species" (i.e., "humans" or "other animals") was selected as an additional filter. Review articles were avoided when possible.
SEARCH RESULTS: The two terms "alcoholism" and "aging" retrieved about 1,350 papers; adding phrases—for example, "postmortem" or "magnetic resonance"—limited the number to fewer than 100 papers. Using the traditional term, "alcoholism" with "dementia" resulted in 876 citations, but using the currently accepted term "alcohol use disorder (AUD)" with "dementia" produced only 87 papers. Similarly, whereas the terms "Alzheimer's" and "alcoholism" yielded 318 results, "Alzheimer's" and "alcohol use disorder (AUD)" returned only 40 citations. As pertinent postmortem pathology papers were published in the 1950s and recent animal models of Alzheimer's disease were created in the early 2000s, articles referenced span the years 1957 to 2024. In total, more than 5,000 articles were considered; about 400 are herein referenced.
DISCUSSION AND CONCLUSIONS: Chronic alcohol misuse accelerates brain aging and contributes to cognitive impairments, including those in the mnemonic domain. The consensus among studies from multiple disciplines, however, is that alcohol misuse can increase the risk for dementia, but not necessarily Alzheimer's disease. Key issues to consider include the reversibility of brain damage following abstinence from chronic alcohol misuse compared to the degenerative and progressive course of Alzheimer's disease, and the characteristic presence of protein inclusions in the brains of people with Alzheimer's disease, which are absent in the brains of those with AUD.

KEYWORDS: alcohol; aging; Alzheimer disease; neuropsychology; neuropathology; magnetic resonance imaging; positron-emission tomography; rodent

In 2020, an estimated 17% of the U.S. population was older than age 65; this proportion is projected to rise to about 23% by 2060.[1,2] This prompts an urgent need for identifying potential and modifiable risk factors contributing to health decline.[3,4] After tobacco, alcohol is the most misused substance in the United States and abroad.[5] Even prior to the coronavirus disease 2019 (COVID-19) pandemic, which contributed to increased drinking rates, alcohol consumption was notably accelerating in several demographic categories, including in men and women older than age 65.[6-8] Consuming alcohol in harmful patterns—such as binge drinking (five or more drinks in men, or four or more drinks in women, in about 2 hours; where a drink is equivalent to 12 oz beer, 5 oz wine, or 1.5 oz distilled spirits)—occurs in more than 25% of older Americans;[5,9] annual growth trends in alcohol misuse are reported to be 2.4% in older men and 1.6% in older women.[10]

Although not causative, older age is a risk factor for dementia: Every 5 years beyond age 65, the risk doubles;[11] and approximately one-third of people over age 85 are diagnosed with dementia.[12,13] Emerging data support alcohol misuse as a risk factor for dementia.[14] This review considers the literature to determine whether chronic alcohol misuse increases the risks for (1) alcohol-related dementias, including Wernicke-Korsakoff syndrome (WKS); (2) Alzheimer's disease; or (3) other forms of dementia (i.e., vascular, frontotemporal, or Lewy body dementia).

Search Methods and Results

Table 1 presents details regarding the literature searches conducted in preparation for this review. For each section in this article, search terms initially included a combination encompassing alcohol use (e.g., alcohol consumption, alcoholism, binge alcohol, alcohol abuse, alcohol use disorder) and cognitive impairment (e.g., dementia, WKS, Alzheimer's disease), which were then narrowed to the relevant topic (e.g., clinical diagnoses, epidemiology, neuropsychology). Several search terms describing alcohol use were used as the more traditional term "alcoholism" resulted in far more citation results than the currently accepted term, "alcohol use disorder (AUD)." For example, the combination of the traditional term "alcoholism" with "dementia" resulted in 876 citations, but using the currently accepted term "alcohol use disorder (AUD)" with "dementia" produced only 87 papers. Similarly, whereas the terms "Alzheimer's" and "alcoholism" yielded 318 results, "Alzheimer's" and "alcohol use disorder (AUD)" returned only 40 citations. The searches also considered subtypes of dementia in addition to Alzheimer's disease, such as alcohol-related WKS and vascular, frontotemporal, and Lewy body dementias. Searches regarding animal models (i.e., rat, mouse) were narrowed by pathological terms or relevant mechanisms (e.g., amyloid, neurofibrillary tangles, presenilin).

The two terms "alcoholism" and "aging" retrieved about 1,350 papers; adding phrases (for example, "postmortem" or "magnetic resonance") limited the number to fewer than 100 papers. As pertinent postmortem pathology papers were published in the 1950s and recent animal models of Alzheimer's disease were created in the early 2000s, articles referenced span the years 1957 to 2024. In total, more than 5,000 articles were considered; approximately 400 are referenced herein (i.e., only articles directly related to search terms were included).

Results of the Reviewed Studies

Human Studies

Clinical diagnoses

Diagnoses of psychiatric illnesses typically rely on use of one of two manuals: the *International Classification of Disease* (*ICD*) first published in 1984 by the World Health Organization (WHO; 11th edition [*ICD-11*] implemented in 2022); or the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) first printed in 1952 by the American Psychiatric Association (fifth edition [*DSM-5*] released in 2013). *ICD* codes are commonly used by primary care physicians, whereas *DSM* codes are more often used by psychiatrists and psychologists. Complicating consistent diagnoses is the evolution over time of concepts underlying clinical diagnoses of alcohol misuse or dementias. Thus, publications have considered diagnosis rates by comparing criteria in *ICD* to *DSM*,[15-17] *ICD* versions,[18,19] *DSM-IV* to *DSM-5* AUD,[20-24] *ICD* AUD,[25] *ICD* neurocognitive disorders,[26] *DSM* neurocognitive disorders;[27] bias in AUD[28,29] and dementia[30-32] diagnoses has also been reviewed.

The diagnosis of an alcohol problem is best made by review of medical histories and interviews with patients. Laboratory tests have low sensitivity, and physical examinations are generally helpful only after the repercussions of alcohol misuse are apparent.[33-35] Consequently, *ICD* diagnoses of AUD in primary care settings typically depend on the presence of health-related conditions, including alcohol-related mental health diagnoses, alcohol-related physical health diagnoses, or evidence for medication prescribed to treat alcohol-related problems.[36] AUD diagnosed using *DSM-5* requires the patient to meet two of 11 criteria; however, specialists—including psychiatrists, psychologists, social workers, and licensed counselors—use *DSM* criteria for diagnosis with questionable consistency.[24] Despite extensive public health efforts by the National Institute on Alcohol Abuse and Alcoholism, the Centers for Disease Control and Prevention, and the U.S. Preventive Services Task Force, current estimates are that fewer than 50% of people who visit primary care providers for alcohol-related issues are asked about the problem. Alcohol screening with validated questionnaires—i.e., the 10-question Alcohol Use Disorders Identification Test

Table 1. Literature Search Details

Relation evaluated	Alcohol consumption and dementia	
Databases used	PubMed, Web of Science, and ScienceDirect	
Literature covered	Clinical diagnoses, epidemiological findings, neuroimaging, neuropsychological profiles, other biomarkers, postmortem pathology, and translational studies	
Literature search dates	January 12, 2023–August 1, 2023	
Literature search terms	"aging," "alcoholism," "alcohol use disorder (AUD)," "brain," "CNS," "dementia," "Wernicke," "Korsakoff," "Alzheimer," "vascular," "frontotemporal," "Lewy body," "clinical," "diagnosis," "epidemiology," "pathology," "autopsy," "postmortem," "histology," "cognitive," "motor," "neuropsychological," "magnetic resonance," "imaging," "PET," "ligand," "degeneration," "atrophy," "translational," "rodent," "rat," "mouse," "model," "amyloid," "neurofibrillary tangles," "α-synuclein," "presenilin"	
Additional filters	Species (i.e., "humans" or "other animals")	
Results*	1,339	"alcoholism" and "aging"
	876	"alcoholism" and "dementia"
	498	"alcohol consumption" and "dementia"
	318	"Alzheimer's" and "alcoholism"
	231	"Alzheimer's" and "alcohol consumption"
	87	"alcohol use disorder (AUD)" and "dementia"
	60	"alcoholism" and "aging" and "magnetic resonance"
	40	"Alzheimer's" and "alcohol use disorder (AUD)"
	31	"alcoholism" and "aging" and "postmortem"

*Source: PubMed, August 14, 2023.

(AUDIT), the 3-question AUDIT-C on consumption, or the 4-question CAGE (Cut down, Annoyed, Guilty, Eye opener)—occurs in only about 2.5% of primary care visits in the United States.[37-39] The Substance Abuse and Mental Health Services Administration (SAMHSA) is another source of alcohol use data based on self-report.[40] As with *ICD* and *DSM* diagnoses, recognized limitations of SAMHSA data include frequent methodological changes (e.g., definitions of alcohol misuse), which hamper longitudinal comparisons.[40] Irrespective of criteria used (i.e., *ICD*, *DSM*, self-report), AUD is underdiagnosed.[37,41,42] Henceforth in this review, "AUD" refers to diagnoses made via any version of *ICD* or *DSM* criteria; otherwise, levels and frequency of alcohol consumption are indicated.

"Dementia" is an umbrella term for a decline in mental (i.e., cognitive, intellectual) functioning that interferes with daily life but does not disturb consciousness or perception. More than 100 subtypes of dementia have been recognized, including proteinopathy (e.g., Alzheimer's, frontotemporal, Lewy body dementia), vascular (i.e., related to blood vessels), and toxic/metabolic (e.g., alcohol-related, WKS) dementias.[43,44] *ICD* added the code for Alzheimer's disease in 1975, and *DSM* added the diagnosis in 1983. Both *ICD-11* and *DSM-5* use the term "neurocognitive impairment" to encompass many types of dementia diagnoses. Diagnosing dementia is difficult owing to its insidious onset as well as the range and diversity of symptoms that can resemble normal aging.[45,46] Indeed, differential diagnoses are imprecise[47,48] as the clinical signs and symptoms of the many dementias are essentially the same;[49,50] criteria and nomenclature for dementia subtypes remain imperfect;[51-53] and selective and specific in vivo biomarkers are still in development.[54,55] Further, as formal dementia differential diagnoses with currently accepted criteria are resource-intensive, up to 85% of dementia diagnoses are made by non-specialist, primary care clinicians.[56]

Epidemiological findings

Patients who develop Alzheimer's disease may initially present with mild cognitive impairment (MCI), defined as a measurable age-accelerated decline in cognition.[57] Among patients with documented MCI, one-third progress to a diagnosis of Alzheimer's disease,[58] which requires the presence of autopsy-detected neuritic plaques and neurofibrillary tangles.[49,57,59] Alzheimer's disease is frequently diagnosed (50% to 75% of dementia cases), but the diagnosis is rarely validated with imaging (i.e., positron emission tomography [PET]) or postmortem examination.[60-63] When autopsies are conducted, between 12% and 23% of patients diagnosed antemortem with Alzheimer's disease do not show defining neuropathology, suggesting that current prevalence estimates of Alzheimer's disease are high.[64,65] Vascular dementia, the second most diagnosed subtype (up to 20% of cases), often coexists with and is incorrectly diagnosed as Alzheimer's disease.[66,67] The

remaining dementias are typically categorized as Lewy body, frontotemporal, or alcohol-related.[68]

Compared with other types, alcohol-related dementia tends to have an early onset (i.e., ages 45 to 64) and slow progress.[69-71] In addition to alcohol-related dementia, thiamine deficiency (i.e., Wernicke's encephalopathy) can occur in settings of high alcohol consumption and in malnutrition due to other causes (e.g., parenteral feeding, bariatric surgery, severe pregnancy-related vomiting).[72,73] The acute nutritional deficiency is reversible if adequately treated but can otherwise advance to WKS characterized by severe, persistent, cognitive impairment predominantly affecting memory.[74] In contrast to Alzheimer's disease, alcohol-related dementia and WKS are more commonly diagnosed in men than women[75-77] and are less likely to be identified as such for several reasons, including underreporting of the extent of alcohol consumption, diagnosis perception bias, and a lack of standardized measures of thiamine.[78,79]

Epidemiological studies support alcohol misuse and AUD as a risk factor for all types of dementia (i.e., collapsed across subtypes). For example, a study in France using *ICD-10* codes to define AUD (codes F10.1–F10.9, Z50.2, F10.20–F10.23) and dementia (codes F00–F03, F05.1, F1x.73, G30, G31, I67.3, R54) found that AUD was a major risk factor for all types, but especially early-onset dementia (before age 65).[77] A Danish cohort comparing people with *ICD-10*–diagnosed alcohol dependence (code F10.2) and dementia (codes F00–F03, G30) with controls matched on sex, date of birth, and municipality reported twice the hazard ratio for dementia among men and women with alcohol dependence.[80] A U.S. study of more than 4,000 women veterans over age 55 that used *ICD-9* codes to define AUD (codes 305.00, 305.01, 303.00, 303.01, 303.02, 303.90, 303.91, 303.92) and dementia (i.e., a comprehensive *ICD-9* code list provided by the Veterans Health Administration)[81] determined that dementia developed in 1.1% of women without AUD and in 3.7% of women with AUD.[60] The United Kingdom Whitehall II study—using alcohol consumption patterns derived from questionnaires and *ICD-10*–defined dementia (codes F00–F03, F05.1, G30, G31)—demonstrated that, compared with people who drank moderately (i.e., 1 to 14 alcohol units/week), those who drank heavily (i.e., more than 14 alcohol units/week) had increased risk for developing *ICD-10* dementia.[82] Similarly, an analysis of seven cohorts from the United Kingdom, France, Sweden, and Finland, using self-reported alcohol consumption metrics and *ICD-10* dementia (codes F00–F03, G30, G31, I20–I25, I61, I63–I66, I67.2, I67.3, I67.4, I67.8, I69.3), found that relative to people who drank moderately (i.e., 1 to 14 drinks/week), those who drank heavily (i.e., more than 14 drinks/week) had a 1.2-fold greater risk of developing dementia; and noted associations between high alcohol consumption and early onset dementia.[83]

With respect to the effects of alcohol misuse and AUD on subtypes of dementia, findings are equivocal. A U.S.-based study using data from commercially insured and Medicare Advantage beneficiaries suggested that AUD (*ICD-9* codes 291*, 303*, 305.0*, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3; *ICD-10* codes F10*, G31.2, G62.1, G72.1, I42.6, K29.2, K70*, K85.2, K86.0, Q86.0) specifically increased the risk for Alzheimer's disease (*ICD-9* code 331.0; *ICD-10* codes F00*, G30*).[84] A study using "driving under the influence" as a proxy for alcohol addiction reported that it was associated with an earlier "Alzheimer's disease" diagnosis; however, the *ICD-9* codes used in this study (i.e., 290.0–290.3, 290.8–290.9, 331.0) were not specific for Alzheimer's dementia.[85] A study using criteria-based diagnoses of dementia and chart-confirmed alcohol misuse (defined as "alcohol consumption that negatively impacts work or social life or leads to legal ramifications") demonstrated that alcohol misuse was a frequent presenting symptom of frontotemporal but not Alzheimer's dementia.[86] Other studies yielded inconclusive results regarding the relationship between alcohol consumption and frontotemporal dementia.[87,88] Moderate to heavy alcohol consumption (i.e., ≥ 7 drinks/week for women, ≥ 14 drinks/week for men) increased the risk for all types of stroke (i.e., ischemic and hemorrhagic stroke) and may thus be a risk factor for vascular dementia,[89-91] but results are inconsistent.[92,93]

In summary, alcohol misuse and AUD increase risk for all types of dementia. Assuming that 20% of AUD goes unrecognized and 20% of dementias are incorrectly classified as Alzheimer's disease, one might speculate that a significant proportion of dementia misclassification includes alcohol-related dementia. Reports that AUD specifically increases Alzheimer's disease likely overestimate the relationship.[94-96]

Neuropsychological profiles

A constellation of executive cognitive functions—including working memory, set shifting (i.e., the ability to unconsciously shift attention between tasks), problem-solving, and attention—are especially vulnerable to the effects of advancing age.[97-99] The neuropsychological profile of AUD uncomplicated by neurological confounders (e.g., WKS, hepatic encephalopathy) also includes deficits in executive functions.[100-102] Additionally, people with uncomplicated AUD show impairments in episodic memory (i.e., the ability to learn, store, and retrieve information about unique personal experiences including time and place),[103] visuospatial processing (i.e., the ability to perceive, analyze, and manipulate visual patterns and images, such as copying complex figures or orienting three-dimensional objects),[104,105] social cognition (i.e., the ability to interpret social information and behave appropriately),[106,107] and gait and balance.[108]

Features of WKS are persistent inability to remember new information (i.e., anterograde amnesia) and occasional confabulation.[74,109] Compared with non-alcohol-related WKS, the neuropsychological profile of alcohol-related WKS is broader and commonly includes executive dysfunction.[110-113]

Meta-analyses suggest that immediate and delayed memory tests (e.g., word-list recall) have high diagnostic accuracy in differentiating people with Alzheimer's disease from individuals

without the disease but poorly discriminate those with and without MCI.[114,115] Among available tools, the Montreal Cognitive Assessment (score ≤ 24), the Mini-Mental State Examination (MMSE, score ≤ 26), and the Dementia Rating Scale (score ≤ 124) appear to be efficient at discriminating MCI from aging without cognitive impairment.[116,117]

Refined neuropsychological data can help distinguish dementia subtypes. For example, people with Alzheimer's disease have more severe deficits in working and delayed memory than do those with WKS.[118-120] In people with AUD or Alzheimer's disease, the degree of impairment in verbal fluency, working memory, and frontal functions can be similar; memory problems, however, are more pronounced in Alzheimer's disease relative to AUD.[121] Similarly, although individuals with alcohol-related dementia or vascular dementia can show executive control deficits, they have less severe memory impairments than observed in those with Alzheimer's disease.[122] Further, patients with alcohol-related dementia demonstrate stabilization of functional impairment with abstinence, whereas those with Alzheimer's disease or vascular dementia show a progressive decline in cognitive functions.[123] Indeed, in a longitudinal study, people with alcohol-related dementia with monitored abstinence showed improved performance on executive functioning tests, whereas people with Alzheimer's disease performed worse on memory tests over the same time spans.[124] The amount of alcohol consumed was unrelated to cognitive performance in patients with *DSM-III*–defined "primary degenerative dementia."[125] In a more recent study of people diagnosed with MCI (*ICD-10* code F067) and evaluated by structured interview for alcohol use—i.e., low (less than 1 drink/week), moderate (1 to 14 drinks/week for men and 1 to 9 drinks/week for women), or heavy (more than 14 drinks/week for men and more than 9 drinks/week for women)—levels of alcohol consumed had no effect on MMSE scores; however, MMSE scores are notoriously insensitive to AUD-related cognitive decline.[126,127]

In summary, neuropsychological profiles differ between people with healthy aging, AUD, WKS, Alzheimer's disease, and other subtypes of dementias. AUD adds a burden to aging in the executive domain. Although AUD, WKS, and Alzheimer's disease all affect memory processes, the effects of Alzheimer's disease on mnemonic functions are greater than those observed in AUD and WKS.

Postmortem neuropathology

Normal aging decreases the brain's viability and increases its vulnerability to damage,[128,129] but neuronal loss is not a salient feature.[130-132] Instead, careful stereological studies have concluded that age-related changes in the central nervous system (CNS) in the cognitively intact, aging brain include alterations to neuron extensions (e.g., retraction of dendritic arbors and synapses);[133,134] deterioration of non-neuronal cells (e.g., oligodendrocytes, astrocytes, microglia);[135-138] and biochemical and molecular changes (e.g., reduced efficacy of neurotransmitters).[139-142] These effects of aging in the healthy brain differ from those seen with pathological aging due to neurological conditions such as Alzheimer's disease.[143,144] A cardinal pathological feature of Alzheimer's CNS tissue, which has been known for more than 100 years, is the progressive accumulation of insoluble fibrous materials, including extracellular plaques of beta-amyloid (A-beta), which has two major isoforms (A-beta-42 and A-beta-40), and intraneuronal neurofibrillary tangles composed of the microtubule-binding protein tau.[145-147] The cause, effect, and reciprocity of A-beta and tau accumulation with neurodegeneration and symptoms of dementia are the subject of ongoing debates.[49,57,59,148] Nevertheless, substantiation of an Alzheimer's diagnosis continues to require postmortem identification of these characteristic protein inclusions in regions including the entorhinal cortex and hippocampus, where they contribute to severe neuronal loss and salient impairment in memory consolidation of newly experienced events.[149,150] Neuropathological observations further suggest that neuronal loss in a specific area of the hippocampus (i.e., subfield CA1) may be a specific marker for Alzheimer's disease.[151-153]

Other proteinopathies also present with neuropathological inclusions. Lewy body dementia is characterized by presence of protein aggregates (Lewy bodies) containing alpha-synuclein,[154] whereas frontotemporal dementia is associated with tau and TDP-43 (transactive DNA binding protein of about 43 kDa) pathology in at least 50% of cases.[155-157] In vascular dementia, gross examination of the brain may reveal overt lesions, microinfarcts, or damage to blood vessels, and microscopic evaluation may detect accumulation of lipids or blood clots.[158,159] Other postmortem signs of vascular disease include white matter atrophy and calcification of arteries.[43,160,161]

A coordinated cross-sectional analysis of six community-based autopsy cohorts in the United States and the United Kingdom highlighted the complexity of the brain pathologies that underlie dementia. The analysis assessed 12 dementia-related pathologies in brains of those age 80 and older, including vascular pathologies (arteriolosclerosis, atherosclerosis, microinfarcts, lacunes, and cerebral amyloid angiopathy); Alzheimer's disease-related pathologies (Braak neurofibrillary tangle stage, Consortium to Establish a Registry for Alzheimer's Disease [CERAD] diffuse plaque score, CERAD neuritic plaque score, and hippocampal sclerosis); Lewy body dementia pathology; and TDP-43 pathology. Of the overall sample, which generally included more women than men, 40% had vascular-related pathology, 70% had Alzheimer's disease-related pathology, and 68% of the cohort had pathology co-occurrence.[162] Smaller studies similarly reported a high frequency of coincident neuropathology.[163,164]

WKS does not have clear neuropathological markers. Careful stereological approaches, however, have demonstrated neuronal loss in medial thalamus, mammillary bodies, pons,

medulla, and anterior-superior vermis of the cerebellum.[165,166] A series of neuropathological analyses compared the effects of alcohol per se to distinct neurological conditions associated with chronic alcohol consumption, including WKS, hepatocerebral degeneration, Marchiafava Bignami disease, and central pontine myelinolysis. The studies concluded that alcohol as such does not contribute to a progressive or irreversible pathology.[118,167-170] Instead, quantitative histological analyses of individuals with uncomplicated AUD often use the term "alcohol-related brain damage" to refer to the plastic CNS changes associated with chronic alcohol use as discrete from neurodegenerative disease.[171,172] Tissue loss occurring mainly in the frontal lobes and cerebellum of the brain in people with AUD is not associated with neuronal death.[173-177] Indeed, no changes in neuron numbers have been documented in brain tissue (e.g., hippocampus, basal ganglia, serotonergic raphe nuclei, cholinergic basal forebrain) from people with AUD without liver pathology, nutritional deficiencies, or other complications.[177-182] AUD-related neuropathological changes are instead largely accounted for by retraction of dendritic arbors and shrinkage of white matter.[173,174,183-188]

Alzheimer's disease-related protein markers (i.e., A-beta, tau) are not affected by alcohol consumption. For example, A-beta plaques were not increased in the brains of people who drank heavily (more than 6 drinks per day for at least 10 years).[189,190] Further, men who drank moderately (not more than 4 drinks/day or 14 drinks/week) showed less neurofibrillary tangle pathology compared with men who drank never or heavily.[191] In a study of individuals with thiamine deficiency who who drank alcohol chronically, neurofibrillary pathology was found in the nucleus basalis (which is affected in WKS) but not in any other brain region.[192] Further, heavy alcohol consumption (i.e., daily, socially disabling alcohol use, and continued drinking despite indisputable health-related or social damage) showed no statistically significant influence on the extent of alpha-synuclein pathology or incidence of total infarcts;[193] however, very heavy alcohol consumption (more than 32 drinks/week) may increase hemorrhagic stroke.[194]

In summary, evidence from postmortem histological analyses indicates that healthy CNS aging and AUD are not associated with significant neuronal loss, whereas Alzheimer's disease and WKS show regionally specific neurodegeneration. Based on postmortem evaluations, uncomplicated AUD does not contribute to archetypal Alzheimer's disease pathology characterized by the presence of protein inclusions.

Neuroimaging biomarkers

An advantage of in vivo neuroimaging over postmortem study is the ability to track individuals longitudinally, which permits evaluation of causative factors in CNS volume changes and the consequences of behavioral modifications (e.g., cessation of alcohol drinking). Cross-sectional and longitudinal magnetic resonance imaging (MRI) studies in adults have provided consistent evidence for systematic, age-related volume increases in spaces filled with cerebrospinal fluid (CSF)—i.e., sulci, fissures, and ventricles—that occur at the expense of gray matter and may accelerate with older age.[195-201] Brain gray matter structures exhibit differential patterns of aging, with convergent longitudinal data indicating an excessive vulnerability of prefrontal cortex.[202-206] Age-related volume deficits in thalamus and cerebellum occur at a slower rate than declines in cortical gray matter.[207-211] Gross white matter volume remains relatively stable across adulthood;[201,212-214] however, appropriate imaging modalities (e.g., fluid-attenuated inversion recovery, diffusion tensor imaging) demonstrate more hyperintense inclusions (i.e., white matter hyperintensities [WMH]),[215-218] and microstructural compromise in older relative to younger individuals.[219-222]

Cross-sectional neuroimaging reports support AUD-related volume shrinkage in specific brain structures, including frontal, temporal, and parietal cortices; diencephalon; brain stem; and cerebellum.[223-229] In contrast to results of postmortem analyses of neuronal numbers, neuroimaging studies describe significant volume deficits in people with AUD, relative to healthy controls, in hippocampus and basal ganglia (i.e., caudate, putamen, nucleus accumbens) that may be accounted for by white matter compromise.[224,230-235] Longitudinal studies that compare individuals with older age at AUD onset and relatively less lifetime alcohol use with individuals with younger age at AUD onset further support accelerated brain aging in frontal cortical volumes due to age–alcohol interactions and not just attributable to more years of alcohol misuse.[227,236-239] Other longitudinal studies show that alcohol abstinence is associated with brain integrity improvement (i.e., volume recovery), whereas relapse precipitates further volume shrinkage.[240-244] Individuals with AUD who relapse show continuing volume decline compared with those who achieve abstinence,[225,241,245,246] but even reduced drinking without achieving or maintaining complete abstinence can improve brain structure and function.[247] Similarly, a controlled longitudinal study that assessed individuals with AUD soon after withdrawal and then again after 2 weeks of sobriety suggested resolution of volume deficits specifically in hippocampal subfield CA2+3[248] (also see Zahr et al., 2019[232]; Lee et al., 2016[249]). This reversibility of volume deficits with abstinence is in stark contrast to the irrevocable progression of Alzheimer's disease.[250,251]

Acute Wernicke's encephalopathy also has characteristic changes evident on transverse relaxation time (T2)-weighted images showing bilateral, high signal intensities in the periaqueductal gray, mammillary bodies, thalamus, and hypothalamus.[252-254] Quantitative MRI documents a graded pattern of accruing volume deficits in hippocampus, thalamus, mammillary bodies, cerebellum, and pons as disease severity progresses from AUD to WKS.[230,255,256] Mammillary body shrinkage has been suggested as being able to differentiate WKS from Alzheimer's disease,[257,258] as have diffusion tensor imaging

(DTI) metrics indicating abnormalities in anterior thalamus to hippocampus white matter tracts.[259]

Deviations of hippocampal volume from normal age-related decline have been identified as a sensitive indicator of Alzheimer's disease pathology.[22,234,260,261] Indeed, atrophy of entorhinal cortex and hippocampus may distinguish Alzheimer's disease from healthy aging with up to 90% accuracy;[262,263] further, the rate and extent of CA1 atrophy may help distinguish Alzheimer's disease from other forms of dementia.[241,264-267] Longitudinal studies suggest that the pattern of gray matter atrophy in people with MCI who are later diagnosed with Alzheimer's disease mimics the pattern of atrophy observed in Alzheimer's disease but is less extreme. However, in people with MCI who do not eventually receive an Alzheimer's disease diagnosis, the pattern of gray matter atrophy is more comparable to that observed in healthy elderly individuals without dementia.[268-270] Similarly, detrimental changes in regional (e.g., fornix, uncinate, cingulum) diffusivity in MCI quantified using DTI are less pronounced than those observed in people with Alzheimer's disease.[114,271,272]

A research framework for diagnosing Alzheimer's disease, released by the National Institute on Aging in 2018, integrated neuroimaging biomarkers A, T, and N. In this framework, A represents A-beta plaques determined by cortical amyloid PET ligand binding (or CSF A-beta-42 levels); T represents fibrillar tau protein, determined by cortical tau PET ligand binding (or CSF phosphorylated tau [p-tau] levels); and N represents neuronal injury or neurodegeneration determined with fluorodeoxyglucose PET hypometabolism or MRI volume (typically hippocampal) atrophy.[273-275] These three markers are used to distinguish among eight dementia profiles: normal, healthy individuals (A-T-N-); people with a condition along the Alzheimer's disease continuum (A+T-N-; A+T-N+; A+T+N-; A+T+N+); and people with non-Alzheimer's changes (A-T+N-; A-T+N+; A-T-N+).[57,276]

Vascular dementias (which include at least six subtypes) are identified on MRI by presence of infarcts, small cavities (lacunes), and WMH.[277-280] WMH are considered a neuroimaging feature of cerebral small vessel disease that can increase the risk for stroke and vascular dementia.[281,282] As they are ubiquitous and heterogeneous, however, a better characterization of the extent, distribution, and cognitive correlates of WMH is necessary.[283-285] In support of a high co-occurrence of Alzheimer's disease and vascular dementias, a literature review found a strong relationship between presence of amyloid and WMH burden[286] (also see Eloyan et al., 2023[287]).

Although separate structural neuroimaging studies in people with AUD, WKS, or Alzheimer's disease report gray matter volume loss in common regions, including hippocampus,[258,288,289] a direct comparison among these patient groups demonstrates that hippocampal volume loss in people with AUD relative to Alzheimer's disease is less severe.[290] Further, PET markers that characterize Alzheimer's disease are not elevated in people with AUD. Two PET studies using the Pittsburgh Compound-B ([^{11}C]PiB) ligand found no significant differences in global A-beta loads between people with AUD and healthy control study participants[291,292] (also see Mendes et al., 2018[293]). Another report found that compared with no drinking, moderate drinking (1 to 13 drinks/week) was associated with lower [^{11}C]PiB-determined A-beta deposition.[294] In contrast, people with AUD had larger WMH volumes than did healthy controls, suggesting an increased cerebrovascular risk in AUD.[207,292]

In summary, healthy aging is characterized by nonlinear gray matter volume decreases, particularly in frontal regions; slower white matter decline; and a greater incidence, compared to younger brains, of WMH.[227,295-298] AUD can amplify the severity and extent of age-related volume decline, especially in frontal regions, but abstinence is associated with significant volume recovery.[246,299] In vivo diagnosis of Alzheimer's disease necessitates PET imaging, but available evidence does not support AUD as contributing to Alzheimer's disease PET markers. In vivo MRI of individuals with Alzheimer's disease can demonstrate greater than age-corrected hippocampal atrophy, but deviations from age-related changes can be challenging to quantify. Instead, emerging data suggest that hippocampal subfield analyses (e.g., effects on CA1 in Alzheimer's disease and on CA2+3 in AUD) may help with future differential diagnoses.

CSF and blood biomarkers

The National Institute on Aging research framework supports CSF quantification of extracellular A-beta-42 and p-tau for accurate and early diagnosis of Alzheimer's disease, but optimization and standardization of these measures is in progress.[300-302] CSF A-beta-42 levels are low in people with Alzheimer's disease compared to unaffected controls and reflect an increase in CNS amyloid plaques.[303-305] Low CSF levels of A-beta-42 also can predict MCI and conversion from MCI to Alzheimer's disease.[306,307] As levels of CSF A-beta-42 are also low in Lewy body, vascular, and frontotemporal dementias, however, A-beta isoforms are being explored to help to differentiate dementia subtypes.[308-310] Levels of CSF tau, p-tau, and their epitopes are high in people with Alzheimer's disease compared to unaffected subjects and may indicate hippocampal atrophy, but levels of these CSF proteins are also high relative to healthy controls in other neurodegenerative diseases.[311-313] Combinations and ratios (e.g., A-beta-42/A-beta-40) of CSF A-beta-42, total tau, and p-tau and their variants are under investigation to improve success of differential diagnoses.[314,315]

Total tau is significantly elevated in people with acute Wernicke's encephalopathy, but the overall pattern of CSF changes (involving A-beta, total tau, and p-tau) can clearly distinguish acute and chronic WKS from Alzheimer's disease.[316] CSF tau and A-beta markers are present in only 11% of AUD patients with cognitive deficits;[317] conversely, alcohol misuse is rarely observed in those with Alzheimer's disease

biomarkers.[318] Thus, CSF tau and A-beta markers may be useful in differentiating alcohol-related cognitive disorders from Alzheimer's disease.[319]

Although neuroimaging and CSF markers approved by the U.S. Food and Drug Administration can aid in detection and diagnosis of Alzheimer's disease, the clinical implementation of these testing modalities is limited because of their availability, cost, and perceived invasiveness.[320] Blood-based markers are also in development for earlier, faster, and more accessible diagnoses.[321] Associations between blood and CSF tau and A-beta and other disease markers, however, and their ability to help with differential diagnoses are not fully established.[322-325]

Summary of human studies

The consensus among studies from multiple disciplines is that AUD can increase the risk for dementia, but not necessarily the risk of Alzheimer's disease. A review of clinical and epidemiological data suggests that criteria and nomenclature of dementia subtypes need improvement. Neuropsychological and biological markers that can differentiate dementia subtypes are in progress but currently limited. Whether alcohol misuse contributes to an added burden on pre-existing Alzheimer's disease remains an open and ongoing research question, which may be approached in animal models. Indeed, basic science strategies that can control alcohol exposure may help clarify controversies, including whether alcohol in the context of genetically induced Alzheimer's disease pathology changes the extent, distribution, or signaling pathways of relevant biomarkers.

Translational Studies

Rodent models of AUD

In contrast to the human brain, the rat brain increases in weight and length with advancing age and demonstrates continued growth in older (e.g., age 763 days) relative to younger (e.g., age 109 days) rodents.[326,327] Longitudinal imaging studies that followed animals for up to 19 months confirm accrual of body weight and total brain volume with increasing age in wild-type Wistar rats, alcohol-preferring (P) and non-preferring (NP) strains derived from Wistar rats, and Fischer 344 (F344) rats.[220,228,328-330] MRI studies further show an aging-related pattern in rats contrary to that observed in humans: Total CSF, gray matter, and white matter volumes continue to increase with older age.[228,331] These fundamental differences in CNS aging between rodents and humans are critical to model in studies that consider the combined effects of ethanol (EtOH) exposure and Alzheimer's disease-related pathology.

Several susceptible brain regions have been demonstrated in rodents exposed to high EtOH levels via intragastric,[332] intraperitoneal (i.p.),[333,334] or vapor[335,336] protocols. Immunohistochemical staining procedures highlight degenerative effects of EtOH on corticolimbic circuitry.[337-342] By contrast, unbiased screening approaches that indicate neuronal activity (e.g., glucose utilization, c-Fos expression) but not loss identify different regions affected by EtOH, including thalamus, colliculi, cerebellum, and pons.[343-346] Longitudinal neuroimaging findings consistently report ventricular enlargement in response to binge and chronic EtOH exposure that is reversible upon abstinence.[228,330,347-349] Indeed, among regions demonstrating reduced volume following EtOH exposure (e.g., retrosplenial and cingulate cortices, dorsal hippocampi, central and ventroposterior thalami, corpus callosum), most show significant recovery with abstinence.[350,351] Volumes of the colliculi and periaqueductal gray, however, show persistent volume deficits with abstinence.[350,351] Although the colliculi may be relevant to human AUD, they have rarely been investigated in humans, possibly because of the challenges in visualizing and quantifying colliculi by MRI.[352]

Relatively few papers have explored the effects of EtOH on the aged rodent brain. Following a single i.p. EtOH dose, older (18 months) compared with younger (postnatal days 70 to 72) Sprague Dawley rats showed greater EtOH-induced ataxia (accelerating rotarod, aerial righting reflex) and cognitive impairment (i.e., longer latency to locate submerged platform on the Morris water maze).[353] However, against expectations, a longitudinal in vivo study of F344 rats exposed to intragastric EtOH for 4 days[354] showed greater transient tissue volume compromise in young rats (age 4 months) compared to older rats (age 17 months).[331] By contrast, EtOH administration alters markers of astrocytes and microglia more significantly in older than younger animals. For example, chronic moderate EtOH exposure (daily 2 g/kg, i.p. doses for 45 days) increased glial fibrillary acidic protein (GFAP, an astrocyte protein expression marker) to a greater extent in older (age 19 months) than younger (age 3 months) Wistar rats.[355] Similarly, a microglial mRNA marker that increased in response to EtOH resolved with abstinence in young but not older C57BL/6J mice[356] (also see Marsland et al., 2022[357]).

Rodent models of Alzheimer's disease

Several genetically modified (i.e., transgenic) mouse models of Alzheimer's disease are now available. The first models used various constructs to overexpress amyloid precursor protein (APP), which is processed in the body by enzymes (i.e., beta- and gamma-secretases) to generate soluble amyloid peptide (A-beta) fragments.[358] Mice with overproduction of total A-beta from APP exhibit extracellular A-beta deposits reminiscent of plaques in human brains as well as cognitive dysfunction.[359-361] However, these animals did not have neurofibrillary tangles or show neuronal loss. Second-generation mutant mice included overexpression of presenilin (PS), a constituent of the gamma-secretase complex that cleaves APP.[362] PS1 overexpression alone did not induce A-beta pathology;[363] however, the combined expression of APP and PS1 increased pathogenic A-beta production and deposition, behavioral deficits, and neuronal

loss.[364-367] One of these models was the 5XFAD mouse line, which expresses five human APP and PS1 transgenes and results in mice with A-beta pathology, gliosis, synaptic degeneration, neuronal loss, and progressive cognitive deficits as early as 4 months of age.[368] Despite their aggressive phenotypes, these models also failed to develop neurofibrillary tangles. In efforts to replicate neurofibrillary tangle pathology, a mouse line was created that carried targeted insertions (knock-in mutations) of PS1, APP, and microtubule-associated protein tau (i.e., 3xTg-AD mice).[369] The 3xTg-AD mouse line is a well-validated animal model that develops rapid, age-dependent, and progressive Alzheimer's-like neuropathology, including A-beta and tau tangles.[370-372]

Although widely used, these models imitate only certain aspects of human Alzheimer's disease pathology.[373-375] Further, the amyloid peptides generated by mice are distinct from those produced by the human brain.[376] Such gaps have led to a program initiated by the National Institute on Aging—the Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (https://www.model-ad.org)—to fund development of Alzheimer's disease mouse models that better recapitulate the human disease.

Rodent models of AUD and Alzheimer's disease

Only a few studies have evaluated how EtOH may exacerbate Alzheimer's-related behavior and brain pathology in wild-type rodents. Compared to unexposed mice, wild-type C57BL/6J mice exposed to EtOH (1 month, free access to water, 10% or 20% EtOH) showed impaired spatial memory and elevated hippocampal p-tau, but no change in total tau.[377] Similarly, wild-type, male C57BL/6J mice exposed to both EtOH (via liquid diet for 7 weeks at 28% of total calories) and thiamine deficiency demonstrated nonspecific, whole-brain increases in A-beta (both A-beta-42 and A-beta-40 isoforms) protein levels compared to unexposed mice[378] (also see Zhao et al., 2011[379]). Finally, compared with unexposed animals, Sprague Dawley rats exposed to EtOH (via liquid diet for 5 weeks at about 36% of total calories) showed increased expression of APP and beta-site APP-cleaving enzyme 1 (BACE1, which is critical for A-beta expression) in hippocampus, cerebellum, and striatum.[380] Of note, nonspecific, elevated levels of A-beta also have been observed in response to other age-related pathologies (e.g., hypertension, diabetes[381,382]), and elevations in p-tau can occur in response to other, particularly anesthetic, psychoactive agents.[383,384]

Findings observed in wild-type animals appear to be exaggerated in transgenic mice. For example, APP/PS1 mice exposed to EtOH (drinking in the dark for 1 month), compared to vehicle-treated APP/PS1 animals, showed greater memory deficits (i.e., Morris water maze performance), higher whole-brain APP and BACE1 levels, and enhanced plaque formation.[385] Similarly, compared with unexposed mice, APP/PS mice exposed to 10 weeks of moderate EtOH in a two-bottle choice design showed deficits in nest building (but not in an object location memory task), and a higher frequency of A-beta deposition and plaques in hippocampus.[386] Also in APP/PS transgenic mice, binge EtOH treatment during adolescence (via four i.p. injections per week of 2.5 g/kg EtOH during postnatal days 20 to 60) increased A-beta RNA and protein expression in the hippocampus at ages 6 and 12 months.[387] In 3xTg-AD mice—the only transgenic model able to produce both A-beta and tau markers—EtOH exposed (via 4-month, free access to water or 25% EtOH), compared with saccharin-exposed (control) 3xTg-AD mice, showed impaired spatial memory on the Morris water maze and upregulated A-beta-42/40, total tau, and p-tau 1 month after EtOH exposure.[388] Another study showed that EtOH exposure (6 weeks of 4 days/week vaporized EtOH) to 3xTg-AD mice hastened cognitive impairment and increased levels of a different protein marker, alpha-synuclein (relevant to Lewy body dementias).[389]

Recent translational work highlights sex differences in the interaction of EtOH with Alzheimer's disease-related pathology. EtOH exposure caused greater cognitive impairment in female than male "middle aged" (ages 6 to 9 months) wild-type C57BL/6J mice,[390] which was associated with an increase in hippocampal amyloid levels.[391] In mice with abnormal tau deposition (i.e., PS19 model with the T34 tau isoform), 16 weeks of intermittent access to water containing 20% EtOH increased the excitability of the locus coeruleus more in female than male mice.[392] Finally, 3xTg-AD adolescent and adult mice exposed to EtOH showed EtOH-related increases in total and hyperphosphorylated tau in female mice but not in male mice, which were hypothesized to be related to impaired lysosome function.[393,394] These recent papers demonstrating EtOH effects in only female transgenic mice[393,394] acknowledged previous findings that total tau and p-tau were increased in both sexes of 3xTg-AD mice,[388] but did not comment on the underlying reasons for such discrepancies. Indeed, the relevance of sex-related findings in transgenic rodents to the human condition await a better understanding of the pathological mechanisms underpinning Alzheimer's disease.

Conclusions

Limitations of the current narrative review are that it failed to address all nuances of the potential relationship between alcohol misuse and dementia risk. For example, the contributions of a genetic predisposition to Alzheimer's disease (i.e., presence of the apolipoprotein E epsilon4 allele, the major genetic risk factor) to the various metrics were not considered.[92,395] Further, an emerging literature showing a relationship between liver pathology—including alcohol-related liver disease—and Alzheimer's disease was not explored.[396-398]

This literature review indicates that chronic alcohol misuse accelerates brain aging and contributes to cognitive impairments, including those in the mnemonic domain also

affected in Alzheimer's disease. The current literature analysis, however, agrees with a 2001 review published in this journal that alcohol misuse does not increase the risk for Alzheimer's disease per se.[399] Whether alcohol misuse or AUD increase the risk for alcohol-related or other forms of dementia may be clarified by improvements in neuropsychological tests or biomarkers better able to differentiate dementias in vivo.

References

1. Vespa J, Armstrong DM, Medina L. Demographic turning points for the United States: Population projections for 2020 to 2060. 2020. *Curr Popul Rep*. https://www.census.gov/library/publications/2020/demo/p25-1144.html.
2. U.S. Census, Public Information Office. Nation Continues to Age as It Becomes More Diverse. 2022. https://www.census.gov/newsroom/press-releases/2022/population-estimates-characteristics.html.
3. Kochanek KD, Xu J, Arias E. Mortality in the United States, 2019. *NCHS Data Brief*. 2020;395:1-8.
4. Mohebi R, Chen C, Ibrahim NE, et al. Cardiovascular disease projections in the United States based on the 2020 Census estimates. *J Am Coll Cardiol*. 2022;80(6):565-578. https://doi.org/10.1016/j.jacc.2022.05.033.
5. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health*. HHS Publication No. PEP20-07-01-001, NSDUH Series H-55. 2020. https://www.samhsa.gov/data.
6. Tevik K, Selbæk G, Engedal K, Seim A, Krokstad S, Helvik AS. Factors associated with alcohol consumption and prescribed drugs with addiction potential among older women and men – the Nord-Trøndelag health study (HUNT2 and HUNT3), Norway, a population-based longitudinal study. *BMC Geriatr*. 2019;19(1):113. https://doi.org/10.1186/s12877-019-1114-2.
7. Varin M, Liu L, Gabrys R, Gariepy G, MacEachern KH, Weeks M. Increased alcohol use, heavy episodic drinking, and suicide ideation during the COVID-19 pandemic in Canada. *Can J Public Health*. 2022:1-11. https://doi.org/10.17269/s41997-022-00689-7.
8. Keyes KM. Age, period, and cohort effects in alcohol use in the United States in the 20th and 21st centuries: Implications for the coming decades. *Alcohol Res*. 2022;42(1):02. https://doi.org/10.35946/arcr.v42.1.02.
9. Hingson RW, Zha W, White AM. Drinking beyond the binge threshold: Predictors, consequences, and changes in the U.S. *Am J Prev Med*. 2017;52(6):717-727. https://doi.org/10.1016/j.amepre.2017.02.014.
10. Breslow RA, Castle IP, Chen CM, Graubard BI. Trends in alcohol consumption among older Americans: National Health Interview Surveys, 1997 to 2014. *Alcohol Clin Exp Res*. 2017;41(5):976-986. https://doi.org/10.1111/acer.13365.
11. Hall CB, Verghese J, Sliwinski M, et al. Dementia incidence may increase more slowly after age 90: Results from the Bronx Aging Study. *Neurology*. 2005;65(6):882-886. https://doi.org/10.1212/01.wnl.0000176053.98907.3f.
12. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement*. 2013;9(1):63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007.
13. Collaborators GDF. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125. https://doi.org/10.1016/s2468-2667(21)00249-8.
14. Jeon KH, Han K, Jeong S-M, et al. Changes in alcohol consumption and risk of dementia in a nationwide cohort in South Korea. *JAMA Network Open*. 2023;6(2):e2254771-e2254771. https://doi.org/10.1001/jamanetworkopen.2022.54771.
15. Lundin A, Waern M, Löve J, Lövestad S, Hensing G, Danielsson AK. Towards ICD-11 for alcohol dependence: Diagnostic agreement with ICD-10, DSM-5, DSM-IV, DSM-III-R and DSM-III diagnoses in a Swedish general population of women. *Drug Alcohol Depend*. 2021;227:108925. https://doi.org/10.1016/j.drugalcdep.2021.108925.
16. Slade T, Mewton L, O'Dean S, et al. DSM-5 and ICD-11 alcohol use disorder criteria in young adult regular drinkers: Lifetime prevalence and age of onset. *Drug Alcohol Depend*. 2021;229(Pt B):109184. https://doi.org/10.1016/j.drugalcdep.2021.109184.
17. First MB, Gaebel W, Maj M, et al. An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5. *World Psychiatry*. 2021;20(1):34-51. https://doi.org/10.1002/wps.20825.
18. Gaebel W, Stricker J, Kerst A. Changes from ICD-10 to ICD-11 and future directions in psychiatric classification. *Dialogues Clin Neurosci*. 2020;22(1):7-15. https://doi.org/10.31887/DCNS.2020.22.1/wgaebel.
19. Yoon J, Chow A. Comparing chronic condition rates using ICD-9 and ICD-10 in VA patients FY2014-2016. *BMC Health Serv Res*. 2017;17(1):572. https://doi.org/10.1186/s12913-017-2504-9.
20. National Institute of Alcohol Abuse and Alcoholism. Alcohol Use Disorder: A Comparison Between DSM–IV and DSM–5. 2021. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm#.
21. Center for Behavioral Health Statistics and Quality. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2016. https://www.ncbi.nlm.nih.gov/books/NBK519697/.
22. Gorbach T, Pudas S, Lundquist A, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiol Aging*. 2017;51:167-176. https://doi.org/10.1016/j.neurobiolaging.2016.12.002.
23. Hasin D, Shmulewitz D, Stohl M, et al. Test-retest reliability of DSM-5 substance disorder measures as assessed with the PRISM-5, a clinician-administered diagnostic interview. *Drug Alcohol Depend*. 2020;216:108294. https://doi.org/10.1016/j.drugalcdep.2020.108294.
24. Cohen BM, Ravichandran C, Öngür D, Harris PQ, Babb SM. Use of DSM-5 diagnoses vs. other clinical information by US academic-affiliated psychiatrists in assessing and treating psychotic disorders. *World Psychiatry*. 2021;20(3):447-448. https://doi.org/10.1002/wps.20903.
25. Saunders JB, Degenhardt L, Reed GM, Poznyak V. Alcohol use disorders in ICD-11: Past, present, and future. *Alcohol Clin Exp Res*. 2019;43(8):1617-1631. https://doi.org/10.1111/acer.14128.
26. Gaebel W, Jessen F, Kanba S. Neurocognitive disorders in ICD-11: The debate and its outcome. *World Psychiatry*. 2018;17(2):229-230. https://doi.org/10.1002/wps.20534.
27. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: The DSM-5 approach. *Nat Rev Neurol*. 2014;10(11):634-642. https://doi.org/10.1038/nrneurol.2014.181.
28. Vickers-Smith R, Justice AC, Becker WC, et al. Racial and ethnic bias in the diagnosis of alcohol use disorder in veterans. *Am J Psychiatry*. 2023;180(6):426-436. https://doi.org/10.1176/appi.ajp.21111097.
29. Parthasarathy S, Chi FW, Metz V, et al. Disparities in the receipt of alcohol brief intervention: The intersectionality of sex, age, and race/ethnicity. *Addiction*. 2023;118(7):1258-1269. https://doi.org/10.1111/add.16195.

30. Misiura MB, Butts B, Hammerschlag B, et al. Intersectionality in Alzheimer's disease: The role of female sex and black American race in the development and prevalence of Alzheimer's disease. *Neurotherapeutics*. 2023;20(4):1019-1036. https://doi.org/10.1007/s13311-023-01408-x.
31. Beydoun MA, Weiss J, Beydoun HA, et al. Pathways explaining racial/ethnic disparities in incident all-cause and Alzheimer's disease dementia among older US men and women. *Alzheimers Dement (N Y)*. 2022;8(1):e12275. https://doi.org/10.1002/trc2.12275.
32. Mattke S, Jun H, Chen E, Liu Y, Becker A, Wallick C. Expected and diagnosed rates of mild cognitive impairment and dementia in the U.S. Medicare population: Observational analysis. *Alzheimers Res Ther*. 2023;15(1):128. https://doi.org/10.1186/s13195-023-01272-z.
33. Verheij C, Haagsma JA, Koch BCP, Segers AEM, Schuit SCE, Rood PPM. Screening for hazardous alcohol use in the emergency department: Comparison of phosphatidylethanol with the Alcohol Use Disorders Identification Test and the Timeline Follow-back. *Alcohol Clin Exp Res*. 2022;46(12):2225-2235. https://doi.org/10.1111/acer.14958.
34. Finanger T, Vaaler AE, Spigset O, et al. Identification of unhealthy alcohol use by self-report and phosphatidylethanol (PEth) blood concentrations in an acute psychiatric department. *BMC Psychiatry*. 2022;22(1):286. https://doi.org/10.1186/s12888-022-03934-y.
35. Uljas E, Jalkanen V, Kuitunen A, Hynninen M, Hästbacka J. Prevalence of risk-drinking in critically ill patients, screened with carbohydrate-deficient transferrin and AUDIT-C score: A retrospective study. *Acta Anaesthesiol Scand*. 2020;64(2):216-223. https://doi.org/10.1111/aas.13484.
36. Rehm J, Heilig M, Gual A. ICD-11 for alcohol use disorders: Not a convincing answer to the challenges. *Alcohol Clin Exp Res*. 2019;43(11):2296-2300. https://doi.org/10.1111/acer.14182.
37. Mintz CM, Hartz SM, Fisher SL, et al. A cascade of care for alcohol use disorder: Using 2015-2019 National Survey on Drug Use and Health data to identify gaps in past 12-month care. *Alcohol Clin Exp Res*. 2021;45(6):1276-1286. https://doi.org/10.1111/acer.14609.
38. Grucza RA, Bello-Kottenstette JK, Mintz CM, Borodovsky JT. The changing landscape of alcohol use disorder and problem drinking in the USA: Implications for primary care. *Fam Pract*. 2020;37(6):870-872. https://doi.org/10.1093/fampra/cmaa066.
39. Chatterton B, Agnoli A, Schwarz EB, Fenton JJ. Alcohol screening during US primary care visits, 2014–2016. *J Gen Intern Med*. 2022;37(15):3848-3852. https://doi.org/10.1007/s11606-021-07369-1.
40. U.S. Department of Health and Human Services. *National Survey on Drug Use and Health 2021*. 2020. NSDUH-2021-DS0001.
41. Spark TL, Adams RS, Hoffmire CA, Forster JE, Brenner LA. Are we undercounting the true burden of mortality related to suicide, alcohol use, or drug use? An analysis using death certificate data from Colorado veterans. *Am J Epidemiol*. 2023;192(5):720-731. https://doi.org/10.1093/aje/kwac194.
42. Manthey J, Kilian C, Schäfer I, Wirth M, Schulte B. Changes in the alcohol-specific disease burden during the COVID-19 pandemic in Germany: Interrupted time series analyses. *Eur J Public Health*. 2023;33(4):645-652. https://doi.org/10.1093/eurpub/ckad103.
43. Mehta RI, Schneider JA. Neuropathology of the common forms of dementia. *Clin Geriatr Med*. 2023;39(1):91-107. https://doi.org/10.1016/j.cger.2022.07.005.
44. Reddy DS, Abeygunaratne HN. Experimental and clinical biomarkers for progressive evaluation of neuropathology and therapeutic interventions for acute and chronic neurological disorders. *Int J Mol Sci*. 2022;23(19):11734. https://doi.org/10.3390/ijms231911734.
45. Robinson L, Tang E, Taylor J-P. Dementia: Timely diagnosis and early intervention. *BMJ*. 2015;350:h3029. https://doi.org/10.1136/bmj.h3029.
46. Dumurgier J, Tzourio C. Epidemiology of neurological diseases in older adults. *Rev Neurol (Paris)*. 2020;176(9):642-648. https://doi.org/10.1016/j.neurol.2020.01.356.
47. Bruun M, Rhodius-Meester HFM, Koikkalainen J, et al. Evaluating combinations of diagnostic tests to discriminate different dementia types. *Alzheimers Dement (Amst)*. 2018;10:509-518. https://doi.org/10.1016/j.dadm.2018.07.003.
48. Tolonen A, Rhodius-Meester HFM, Bruun M, et al. Data-driven differential diagnosis of dementia using multiclass Disease State Index classifier. *Front Aging Neurosci*. 2018;10:111. https://doi.org/10.3389/fnagi.2018.00111.
49. Knopman DS, Petersen RC, Jack CR Jr. A brief history of "Alzheimer disease": Multiple meanings separated by a common name. *Neurology*. 2019;92(22):1053-1059. https://doi.org/10.1212/wnl.0000000000007583.
50. Bernstein Sideman A, Chalmer R, Ayers E, et al. Lessons from detecting cognitive impairment including dementia (DetectCID) in primary care. *J Alzheimers Dis*. 2022;86(2):655-665. https://doi.org/10.3233/jad-215106.
51. Cerullo E, Quinn TJ, McCleery J, Vounzoulaki E, Cooper NJ, Sutton AJ. Interrater agreement in dementia diagnosis: A systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2021;36(8):1127-1147. https://doi.org/10.1002/gps.5499.
52. Pelegrini LNC, Mota GMP, Ramos CF, Jesus E, Vale FAC. Diagnosing dementia and cognitive dysfunction in the elderly in primary health care: A systematic review. *Dement Neuropsychol*. 2019;13(2):144-153. https://doi.org/10.1590/1980-57642018dn13-020002.
53. Davis KAS, Mueller C, Ashworth M, et al. What gets recorded, counts: Dementia recording in primary care compared with a specialist database. *Age Ageing*. 2021;50(6):2206-2213. https://doi.org/10.1093/ageing/afab164.
54. Teunissen CE, Kimble L, Bayoumy S, et al. Methods to discover and validate biofluid-based biomarkers in neurodegenerative dementias. *Mol Cell Proteomics*. 2023:100629. https://doi.org/10.1016/j.mcpro.2023.100629.
55. Asanomi Y, Shigemizu D, Akiyama S, et al. Dementia subtype prediction models constructed by penalized regression methods for multiclass classification using serum microRNA expression data. *Sci Rep*. 2021;11(1):20947. https://doi.org/10.1038/s41598-021-00424-1.
56. Drabo EF, Barthold D, Joyce G, Ferido P, Chang Chui H, Zissimopoulos J. Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries. *Alzheimers Dement*. 2019;15(11):1402-1411. https://doi.org/10.1016/j.jalz.2019.07.005.
57. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. https://doi.org/10.1016/j.jalz.2018.02.018.
58. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;119(4):252-265. https://doi.org/10.1111/j.1600-0447.2008.01326.x.
59. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Science Transl Med*. 2020;12(524):eaau5732. https://doi.org/10.1126/scitranslmed.aau5732.
60. Bahorik A, Bobrow K, Hoang T, Yaffe K. Increased risk of dementia in older female US veterans with alcohol use disorder. *Addiction*. 2021;116(8):2049-2055. https://doi.org/10.1111/add.15416.
61. Weiner MW. *The Use of MRI and PET for Clinical Diagnosis of Dementia and Investigation of Cognitive Impairment: A Consensus Report*. 2022.
62. Butler E, Mounsey A. Structural MRI for the early diagnosis of Alzheimer disease in patients with MCI. *Am Fam Physician*. 2021;103(5):273-274.

63. Schliep KC, Ju S, Foster NL, et al. How good are medical and death records for identifying dementia? *Alzheimers Dement*. 2022;18(10):1812-1823. https://doi.org/10.1002/alz.12526.
64. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol*. 2012;71(4):266-273. https://doi.org/10.1097/NEN.0b013e31824b211b.
65. Gaugler JE, Ascher-Svanum H, Roth DL, Fafowora T, Siderowf A, Beach TG. Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: An analysis of the NACC-UDS database. *BMC Geriatr*. 2013;13(1):137. https://doi.org/10.1186/1471-2318-13-137.
66. Grodstein F, Leurgans SE, Capuano AW, Schneider JA, Bennett DA. Trends in postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years. *JAMA Neurol*. 2023;80(4):370-376. https://doi.org/10.1001/jamaneurol.2022.5416.
67. Wiese LAK, Gibson A, Guest MA, et al. Global rural health disparities in Alzheimer's disease and related dementias: State of the science. *Alzheimers Dement*. 2023;19(9):4204-4225. https://doi.org/10.1002/alz.13104.
68. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement*. 2017;13(1):28-37. https://doi.org/10.1016/j.jalz.2016.04.002.
69. Gupta S, Warner J. Alcohol-related dementia: A 21st-century silent epidemic? *Br J Psychiatry*. 2008;193(5):351-353. https://doi.org/10.1192/bjp.bp.108.051425.
70. Draper B, Karmel R, Gibson D, Peut A, Anderson P. Alcohol-related cognitive impairment in New South Wales hospital patients aged 50 years and over. *Aust N Z J Psychiatry*. 2011;45(11):985-992. https://doi.org/10.3109/00048674.2011.610297.
71. Cations M, Draper B, Low L-F, et al. Non-genetic risk factors for degenerative and vascular young onset dementia: Results from the INSPIRED and KGOW studies. *J Alzheimers Dis*. 2018;62(4):1747-1758. https://doi.org/10.3233/JAD-171027.
72. Zahr NM, Kaufman KL, Harper CG. Clinical and pathological features of alcohol-related brain damage. *Nat Rev Neurol*. 2011;7(5):284-294. https://doi.org/10.1038/nrneurol.2011.42.
73. Oudman E, Wijnia JW, Oey MJ, van Dam M, Postma A. Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports. *J Neurol Sci*. 2021;426:117482. https://doi.org/10.1016/j.jns.2021.117482.
74. Kopelman MD. What is the Korsakoff syndrome? - A paper in tribute to Prof Alwyn Lishman. *Cogn Neuropsychiatry*. 2022;27(4):296-313. https://doi.org/10.1080/13546805.2022.2067472.
75. Walters S, Contreras AG, Eissman JM, et al. Associations of sex, race, and apolipoprotein E alleles with multiple domains of cognition among older adults. *JAMA Neurol*. 2023;80(9):929-939. https://doi.org/10.1001/jamaneurol.2023.2169.
76. Huque H, Eramudugolla R, Chidiac B, et al. Could country-level factors explain sex differences in dementia incidence and prevalence? A systematic review and meta-analysis. *J Alzheimers Dis*. 2023;91(4):1231-1241. https://doi.org/10.3233/JAD-220724.
77. Schwarzinger M, Pollock BG, Hasan OSM, Dufouil C, Rehm J; QalyDays Study Group. Contribution of alcohol use disorders to the burden of dementia in France 2008-13: A nationwide retrospective cohort study. *Lancet Public Health*. 2018;3(3):e124-e132. https://doi.org/10.1016/S2468-2667(18)30022-7.
78. Palm A, Vataja R, Talaslahti T, et al. Incidence and mortality of alcohol-related dementia and Wernicke-Korsakoff syndrome: A nationwide register study. *Int J Geriatr Psychiatry*. 2022;37(8). https://doi.org/10.1002/gps.5775.
79. Mateus R, Wick JY. Alcohol-related dementia: Rethink how much you drink. *Sr Care Pharm*. 2021;36(7):324-330. https://doi.org/10.4140/TCP.n.2021.324.
80. Holst C, Tolstrup JS, Sørensen HJ, Becker U. Alcohol dependence and risk of somatic diseases and mortality: A cohort study in 19 002 men and women attending alcohol treatment. *Addiction*. 2017;112(8):1358-1366. https://doi.org/10.1111/add.13799.
81. U.S. Department of Veterans Affairs. *VHA Dementia Steering Committee Recommendations for Dementia Care in the VHA Health Care System*. 2016.
82. Sabia S, Fayosse A, Dumurgier J, et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. *BMJ*. 2018;362:k2927. https://doi.org/10.1136/bmj.k2927.
83. Kivimaki M, Singh-Manoux A, Batty GD, et al. Association of alcohol-induced loss of consciousness and overall alcohol consumption with risk for dementia. *JAMA Netw Open*. 2020;3(9):e2016084. https://doi.org/10.1001/jamanetworkopen.2020.16084.
84. Zhang P, Edenberg HJ, Nurnberger J, Lai D, Cheng F, Liu Y. Alcohol use disorder is associated with higher risks of Alzheimer's and Parkinson's diseases: A study of US insurance claims data. *Alzheimers Dement (Amst)*. 2022;14(1):e12370. https://doi.org/10.1002/dad2.12370.
85. Miller M, Orwat D, Rahimi G, Mintzer J. A retrospective, population-based cohort study of driving under the influence, Alzheimer's disease diagnosis, and survival. *Int Psychogeriatr*. 2019;31(4):571-577. https://doi.org/10.1017/s1041610218001151.
86. de Paula França Resende E, Ketelle R, Karydas A, et al. Late-onset alcohol abuse as a presenting symptom of neurodegenerative diseases. *J Alzheimers Dis*. 2022;86(3):1073-1080. https://doi.org/10.3233/JAD-215369.
87. Tremolizzo L, Bianchi E, Susani E, et al. Voluptuary habits and risk of frontotemporal dementia: A case control retrospective study. *J Alzheimers Dis*. 2017;60(2):335-340. https://doi.org/10.3233/jad-170260.
88. Funayama M, Nakajima A, Kurose S, Takata T. Putative alcohol-related dementia as an early manifestation of right temporal variant of frontotemporal dementia. *J Alzheimers Dis*. 2021;83(2):531-537. https://doi.org/10.3233/jad-210501.
89. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: A systematic review. *Age Ageing*. 2008;37(5):505-512. https://doi.org/10.1093/ageing/afn095.
90. Volpe R, Sotis G, Cianciabella M. Is it always Alzheimer's? Let's talk to our patients about "cardiocerebrovascular" prevention. *Aging Clin Exp Res*. 2016;28(1):159-160. https://doi.org/10.1007/s40520-015-0480-7.
91. Smyth A, O'Donnell M, Rangarajan S, et al. Alcohol intake as a risk factor for acute stroke: The INTERSTROKE Study. *Neurology*. 2023;100(2):e142-e153. https://doi.org/10.1212/wnl.0000000000201388.
92. Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA*. 2003;289(11):1405-1413. https://doi.org/10.1001/jama.289.11.1405.
93. Ruitenberg A, van Swieten JC, Witteman JCM, et al. Alcohol consumption and risk of dementia: The Rotterdam Study. *Lancet*. 2002;359(9303):281-286. https://doi.org/10.1016/S0140-6736(02)07493-7.
94. Rochoy M, Gautier S, Béné J, Bordet R, Chazard E. Evolution of dementia related to the use of alcohol in the French nationwide discharge summary database between 2007 and 2017. *Am J Alzheimers Dis Other Demen*. 2019;34(3):188-192. https://doi.org/10.1177/1533317518822043.
95. Mewton L, Visontay R, Hoy N, et al. 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*. 2023;118(3):412-424. https://doi.org/10.1111/add.16035.

96. Mehta RI, Schneider JA. What is 'Alzheimer's disease'? The neuropathological heterogeneity of clinically defined Alzheimer's dementia. *Curr Opin Neurol*. 2021;34(2):237-245. https://doi.org/10.1097/wco.0000000000000912.
97. Indahlastari A, Hardcastle C, Albizu A, et al. A systematic review and meta-analysis of transcranial direct current stimulation to remediate age-related cognitive decline in healthy older adults. *Neuropsychiatr Dis Treat*. 2021;17:971-990. https://doi.org/10.2147/ndt.S259499.
98. Greenwood PM. The frontal aging hypothesis evaluated. *J Int Neuropsychol Soc*. 2000;6(6):705-726. https://doi.org/10.1017/s1355617700666092.
99. Zanto TP, Gazzaley A. Aging of the frontal lobe. *Handb Clin Neurol*. 2019;163:369-389. https://doi.org/10.1016/b978-0-12-804281-6.00020-3.
100. Moggi F, Ossola N, Graser Y, Soravia LM. Trail Making Test: Normative data for patients with severe alcohol use disorder. *Subst Use Misuse*. 2020;55(11):1790-1799. https://doi.org/10.1080/10826084.2020.1765806.
101. Le Berre AP, Fama R, Sullivan EV. Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: A critical review to inform future research. *Alcohol Clin Exp Res*. 2017;41(8):1432-1443. https://doi.org/10.1111/acer.13431.
102. Sullivan EV, Lannoy S, LeBerre AP, Fama R, Pfefferbaum A. Alcohol drinking and alcohol use disorder across the ages: Dynamic effects on the brain and function. In: Brown GG, King TZ, Haaland KY, Crosson B, eds. *APA Handbook of Neuropsychology. Volume 1. Neurobehavioral Disorders and Conditions: Accepted Science and Open Questions*. Washington, DC: American Psychological Association; 2023:569-607. https://doi.org/10.1037/0000307-027.
103. Fama R, Le Berre AP, Hardcastle C, et al. Neurological, nutritional and alcohol consumption factors underlie cognitive and motor deficits in chronic alcoholism. *Addict Biol*. 2019;24(2):290-302. https://doi.org/10.1111/adb.12584.
104. Kaur P, Sidana A, Malhotra N, Gupta A. Effects of abstinence of alcohol on neurocognitive functioning in patients with alcohol dependence syndrome. *Asian J Psychiatr*. 2020;50:101997. https://doi.org/10.1016/j.ajp.2020.101997.
105. Fein G, Shimotsu R, Chu R, Barakos J. Parietal gray matter volume loss is related to spatial processing deficits in long-term abstinent alcoholic men. *Alcohol Clin Exp Res*. 2009;33(10):1806-1814. https://doi.org/10.1111/j.1530-0277.2009.01019.x.
106. Pabst A, Gautier M, Maurage P. Tasks and investigated components in social cognition research among adults with alcohol use disorder: A critical scoping review. *Psychol Addict Behav*. 2022;36(8):999-1011. https://doi.org/10.1037/adb0000874.
107. Lewis B, Garcia CC, Price JL, Schweizer S, Nixon SJ. Cognitive training in recently-abstinent individuals with alcohol use disorder improves emotional stroop performance: Evidence from a randomized pilot trial. *Drug Alcohol Depend*. 2022;231:109239. https://doi.org/10.1016/j.drugalcdep.2021.109239.
108. Sullivan EV, Zahr NM, Sassoon SA, Pfefferbaum A. Disturbed sensory physiology underlies poor balance and disrupts activities of daily living in alcohol use disorder. *Addict Biol*. 2021;26(4):e12966. https://doi.org/10.1111/adb.12966.
109. Bajo A, Fleminger S, Metcalfe C, Kopelman MD. Confabulation: What is associated with its rise and fall? A study in brain injury. *Cortex*. 2017;87:31-43. https://doi.org/10.1016/j.cortex.2016.06.016.
110. Van Oort R, Kessels RPC. Executive dysfunction in Korsakoff's syndrome: Time to revise the DSM criteria for alcohol-induced persisting amnestic disorder? *Int J Psychiatry Clin Pract*. 2009;13(1):78-81. https://doi.org/10.1080/13651500802308290.
111. Oscar-Berman M, Kirkley SM, Gansler DA, Couture A. Comparisons of Korsakoff and non-Korsakoff alcoholics on neuropsychological tests of prefrontal brain functioning. *Alcohol Clin Exp Res*. 2004;28(4):667-675. https://doi.org/10.1097/01.alc.0000122761.09179.b9.
112. Nikolakaros G, Ilonen T, Kurki T, Paju J, Papageorgiou SG, Vataja R. Non-alcoholic Korsakoff syndrome in psychiatric patients with a history of undiagnosed Wernicke's encephalopathy. *J Neurol Sci*. 2016;370:296-302. https://doi.org/10.1016/j.jns.2016.09.025.
113. Nikolakaros G, Kurki T, Paju J, Papageorgiou SG, Vataja R, Ilonen T. Korsakoff syndrome in non-alcoholic psychiatric patients. Variable cognitive presentation and impaired frontotemporal connectivity. *Front Psychiatry*. 2018;9:204. https://doi.org/10.3389/fpsyt.2018.00204.
114. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(3):126-135. https://doi.org/10.1212/wnl.0000000000004826.
115. Weissberger GH, Strong JV, Stefanidis KB, Summers MJ, Bondi MW, Stricker NH. Diagnostic accuracy of memory measures in Alzheimer's dementia and mild cognitive impairment: A systematic review and meta-analysis. *Neuropsychol Rev*. 2017;27(4):354-388. https://doi.org/10.1007/s11065-017-9360-6.
116. Hemmy LS, Linskens EJ, Silverman PC, et al. Brief cognitive tests for distinguishing clinical Alzheimer-type dementia from mild cognitive impairment or normal cognition in older adults with suspected cognitive impairment. *Ann Intern Med*. 2020;172(10):678-687. https://doi.org/10.7326/m19-3889.
117. Yang Y-W, Hsu K-C, Wei C-Y, Tzeng R-C, Chiu P-Y. Operational determination of subjective cognitive decline, mild cognitive impairment, and dementia using sum of boxes of the Clinical Dementia Rating Scale. *Front Aging Neurosci*. 2021;13:705782. https://doi.org/10.3389/fnagi.2021.705782.
118. Kopelman MD. Frontal dysfunction and memory deficits in the alcoholic Korsakoff syndrome and Alzheimer-type dementia. *Brain*. 1991;114 (Pt 1A):117-137.
119. Moss MB, Albert MS, Butters N, Payne M. Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. *Arch Neurol*. 1986;43(3):239-246. https://doi.org/10.1001/archneur.1986.00520030031008.
120. Fama R, Marsh L, Sullivan EV. Dissociation of remote and anterograde memory impairment and neural correlates in alcoholic Korsakoff syndrome. *J Int Neuropsychol Soc*. 2004;10(3):427-441. https://doi.org/10.1017/S135561770410310X.
121. Liappas I, Theotoka I, Kapaki E, Ilias I, Paraskevas GP, Soldatos CR. Neuropsychological assessment of cognitive function in chronic alcohol-dependent patients and patients with Alzheimer's disease. *In Vivo*. 2007;21(6):1115-1118.
122. Schmidt KS, Gallo JL, Ferri C, et al. The neuropsychological profile of alcohol-related dementia suggests cortical and subcortical pathology. *Dement Geriatr Cogn Disord*. 2005;20(5):286-291. https://doi.org/10.1159/000088306.
123. Oslin DW, Cary MS. Alcohol-related dementia: Validation of diagnostic criteria. *Am J Geriatr Psychiatry*. 2003;11(4):441-447. https://doi.org/10.1097/00019442-200307000-00007.
124. Clergue-Duval V, Barré T, Cognat E, et al. Patients with severe alcohol-related cognitive impairment improve in flexibility when abstinence is maintained: A comparative study with Alzheimer's disease. *Front Psychol*. 2022;13:936639. https://doi.org/10.3389/fpsyg.2022.936639.
125. Teri L, Hughes JP, Larson EB. Cognitive deterioration in Alzheimer's disease: Behavioral and health factors. *J Gerontol*. 1990;45(2):P58-63. https://doi.org/10.1093/geronj/45.2.p58.
126. Tsevis T, Westman E, Poulakis K, et al. Demographic and clinical characteristics of individuals with mild cognitive impairment related to grade of alcohol consumption. *Dement Geriatr Cogn Disord*. 2021;50(5):491-497. https://doi.org/10.1159/000519736.

127. Saxton J, Munro CA, Butters MA, Schramke C, McNeil MA. Alcohol, dementia, and Alzheimer's disease: Comparison of neuropsychological profiles. *J Geriatr Psychiatry Neurol*. 2000;13(3): 141-149. https://doi.org/10.1177/089198870001300308.
128. Bourliére F. The comparative biology of ageing: A physiological approach. In: Wolstenholme EW, O'Connor CM, eds. *CIBA Foundation Colloquia on Ageing*. Little, Brown, and Co.; 1957. https://doi.org/10.1002/9780470719039.ch3.
129. Park DC, Festini SB. Theories of memory and aging: A look at the past and a glimpse of the future. *J Gerontol B Psychol Sci Soc Sci*. 2017;72(1):82-90. https://doi.org/10.1093/geronb/gbw066.
130. Pakkenberg B, Gundersen HJ. Solutions to old problems in the quantitation of the central nervous system. *J Neurol Sci*. 1995;129 Suppl:65-67. https://doi.org/10.1016/0022-510x(95)00067-c.
131. Stark AK, Toft MH, Pakkenberg H, et al. The effect of age and gender on the volume and size distribution of neocortical neurons. *Neuroscience*. 2007;150(1):121-130. https://doi.org/10.1016/j.neuroscience.2007.06.062.
132. Walløe S, Pakkenberg B, Fabricius K. Stereological estimation of total cell numbers in the human cerebral and cerebellar cortex. *Front Hum Neurosci*. 2014;8:508. https://doi.org/10.3389/fnhum.2014.00508.
133. Nakamura S, Akiguchi I, Kameyama M, Mizuno N. Age-related changes of pyramidal cell basal dendrites in layers III and V of human motor cortex: A quantitative Golgi study. *Acta Neuropathol*. 1985;65(3-4):281-284. https://doi.org/10.1007/bf00687009.
134. Tang Y, Nyengaard JR, De Groot DM, Gundersen HJ. Total regional and global number of synapses in the human brain neocortex. *Synapse*. 2001;41(3):258-273. https://doi.org/10.1002/syn.1083.
135. Andersen BB, Gundersen HJG, Pakkenberg B. Aging of the human cerebellum: A stereological study. *J Comp Neurol*. 2003;466(3):356-365. https://doi.org/10.1002/cne.10884.
136. Pakkenberg B, Pelvig D, Marner L, et al. Aging and the human neocortex. *Exp Gerontol*. 2003;38(1-2):95-99. https://doi.org/10.1016/s0531-5565(02)00151-1.
137. Kemper TL. Neuroanatomical and neuropathological changes during aging and dementia. In: Albert ML, Knoefel JE, eds. *Clinical Neurology of Aging*. 2nd ed. New York, NY: Oxford University Press; 1994:3-67.
138. Rommer PS, Bsteh G, Zrzavy T, Hoeftberger R, Berger T. Immunosenescence in neurological diseases-Is there enough evidence? *Biomedicines*. 2022;10(11):2864. https://doi.org/10.3390/biomedicines10112864.
139. Glorioso C, Sibille E. Between destiny and disease: Genetics and molecular pathways of human central nervous system aging. *Prog Neurobiol*. 2011;93(2):165-181. https://doi.org/10.1016/j.pneurobio.2010.11.006.
140. Martínez G, Khatiwada S, Costa-Mattioli M, Hetz C. ER proteostasis control of neuronal physiology and synaptic function. *Trends Neurosci*. 2018;41(9):610-624. https://doi.org/10.1016/j.tins.2018.05.009.
141. Grimm A. Impairments in brain bioenergetics in aging and tau pathology: A chicken and egg situation? *Cells*. 2021;10(10):2531. https://doi.org/10.3390/cells10102531.
142. Jin M, Cai S-Q. Mechanisms underlying brain aging under normal and pathological conditions. *Neurosci Bull*. 2023;39(2):303-314. https://doi.org/10.1007/s12264-022-00969-9.
143. Kowalska M, Owecki M, Prendecki M, et al. Aging and neurological diseases. In: Dorszewska J, Kozubski W, eds. *Senescence – Physiology or Pathology*. Rijeka, Croatia: IntechOpen; 2017:63-94. https://doi.org/10.5772/65533.
144. Cai J, Sun J, Chen H, et al. Different mechanisms in periventricular and deep white matter hyperintensities in old subjects. *Front Aging Neurosci*. 2022;14:940538. https://doi.org/10.3389/fnagi.2022.940538.
145. Castaño EM, Frangione B. Human amyloidosis, Alzheimer disease and related disorders. *Lab Invest*. 1988;58(2):122-132. https://doi.org/10.1097/00002093-198802030-00103.
146. Braak H, Braak E. Morphology of the human isocortex in young and aged individuals: Qualitative and quantitative findings. *Interdiscip Top Gerontol Geriatr*. 1988;25:1-15. https://doi.org/10.1159/000416145.
147. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde." *Clin Anat*. 1995;8(6): 429-431. https://doi.org/10.1002/ca.980080612.
148. Chételat G. Alzheimer disease: Aβ-independent processes–rethinking preclinical AD. *Nat Rev Neurol*. 2013;9(3):123-124. https://doi.org/10.1038/nrneurol.2013.21.
149. Ferreira D, Perestelo-Pérez L, Westman E, Wahlund LO, Sarría A, Serrano-Aguilar P. Meta-review of CSF core biomarkers in Alzheimer's disease: The state-of-the-art after the new revised diagnostic criteria. *Front Aging Neurosci*. 2014;6:47. https://doi.org/10.3389/fnagi.2014.00047.
150. Driscoll I, Troncoso JC, Rudow G, et al. Correspondence between in vivo (11)C-PiB-PET amyloid imaging and postmortem, region-matched assessment of plaques. *Acta Neuropathol*. 2012;124(6): 823-831. https://doi.org/10.1007/s00401-012-1025-1.
151. Braak E, Braak H. Alzheimer's disease: Transiently developing dendritic changes in pyramidal cells of sector CA1 of the Ammon's horn. *Acta Neuropathol*. 1997;93(4):323-325. https://doi.org/10.1007/s004010050622.
152. Saito Y, Murayama S. Neuropathology of mild cognitive impairment. *Neuropathology*. 2007;27(6):578-584. https://doi.org/10.1111/j.1440-1789.2007.00806.x.
153. West MJ, Kawas CH, Stewart WF, Rudow GL, Troncoso JC. Hippocampal neurons in pre-clinical Alzheimer's disease. *Neurobiol Aging*. 2004;25(9):1205-1212. https://doi.org/10.1016/j.neurobiolaging.2003.12.005.
154. Martin WRW, Younce JR, Campbell MC, et al. Neocortical Lewy body pathology parallels Parkinson's dementia, but not always. *Ann Neurol*. 2023;93(1):184-195. https://doi.org/10.1002/ana.26542.
155. Schneider JA. Neuropathology of dementia disorders. *Continuum (Minneap Minn)*. 2022;28(3):834-851. https://doi.org/10.1212/con.0000000000001137.
156. Cordts I, Wachinger A, Scialo C, et al. TDP-43 proteinopathy specific biomarker development. *Cells*. 2023;12(4):597. https://doi.org/10.3390/cells12040597.
157. Virgilio E, De Marchi F, Contaldi E, et al. The role of tau beyond Alzheimer's disease: A narrative review. *Biomedicines*. 2022;10(4):760. https://doi.org/10.3390/biomedicines10040760.
158. Hase Y, Horsburgh K, Ihara M, Kalaria RN. White matter degeneration in vascular and other ageing-related dementias. *J Neurochem*. 2018;144(5):617-633. https://doi.org/10.1111/jnc.14271.
159. Huang J, Biessels GJ, de Leeuw FE, et al. Cerebral microinfarcts revisited: Detection, causes, and clinical relevance. *Int J Stroke*. 2024;19(1):7-15. https://doi.org/10.1177/17474930231187979.
160. Beach TG, Sue LI, Scott S, et al. Cerebral white matter rarefaction has both neurodegenerative and vascular causes and may primarily be a distal axonopathy. *J Neuropathol Exp Neurol*. 2023;82(6):457-466. https://doi.org/10.1093/jnen/nlad026.
161. Ramonet D, de Yebra L, Fredriksson K, Bernal F, Ribalta T, Mahy N. Similar calcification process in acute and chronic human brain pathologies. *J Neurosci Res*. 2006;83(1):147-156. https://doi.org/10.1002/jnr.20711.
162. Nichols E, Merrick R, Hay SI, et al. The prevalence, correlation, and co-occurrence of neuropathology in old age: Harmonisation of 12 measures across six community-based autopsy studies of dementia. *Lancet Healthy Longev*. 2023;4(3):e115-e125. https://doi.org/10.1016/s2666-7568(23)00019-3.
163. Nelson RS, Abner EL, Jicha GA, et al. Neurodegenerative pathologies associated with behavioral and psychological symptoms of dementia in a community-based autopsy cohort. *Acta Neuropathol Commun*. 2023;11(1):89. https://doi.org/10.1186/s40478-023-01576-z.

164. Robinson JL, Xie SX, Baer DR, et al. Pathological combinations in neurodegenerative disease are heterogeneous and disease-associated. *Brain*. 2023;146(6):2557-2569. https://doi.org/10.1093/brain/awad059.
165. Harper C. The neuropathology of alcohol-related brain damage. *Alcohol Alcohol*. 2009;44(2):136-140. https://doi.org/10.1093/alcalc/agn102.
166. Sheedy D, Lara A, Garrick T, Harper C. Size of mamillary bodies in health and disease: Useful measurements in neuroradiological diagnosis of Wernicke's encephalopathy. *Alcohol Clin Exp Res*. 1999;23(10):1624-1628. https://doi.org/10.1111/j.1530-0277.1999.tb04053.x.
167. Lishman WA. Alcoholic dementia: A hypothesis. *Lancet*. 1986;1(8491):1184-1186. https://doi.org/10.1016/s0140-6736(86)91162-1.
168. Acker C, Jacobson RR, Lishman WA. Memory and ventricular size in alcoholics. *Psychol Med*. 1987;17(2):343-348. https://doi.org/10.1017/s0033291700024880.
169. Adams RD, Victor M, Mancall EL. Central pontine myelinolysis: A hitherto undescribed disease occurring in alcoholic and malnourished patients. *AMA Arch Neurol Psychiatry*. 1959;81(2):154-172.
170. Victor M, Brausch C. The role of abstinence in the genesis of alcoholic epilepsy. *Epilepsia*. 1967;8(1):1-20. https://doi.org/10.1111/j.1528-1157.1967.tb03815.x.
171. Sutherland GT, Sheedy D, Kril JJ. Neuropathology of alcoholism. *Handb Clin Neurol*. 2014;125:603-615. https://doi.org/10.1016/b978-0-444-62619-6.00035-5.
172. Sutherland GT, Sheedy D, Kril JJ. Using autopsy brain tissue to study alcohol-related brain damage in the genomic age. *Alcohol Clin Exp Res*. 2014;38(1):1-8. https://doi.org/10.1111/acer.12243.
173. Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*. 1997;79(4):983-998. https://doi.org/10.1016/s0306-4522(97)00083-3.
174. Harper CG, Daly J, Kril J. Brain water in chronic alcoholics: A necropsy study. *Lancet*. 1985;2(8450):327. https://doi.org/10.1016/s0140-6736(85)90368-x.
175. Darke S, Duflou J, Torok M, Prolov T. Toxicology, circumstances, and pathology of deaths from acute alcohol toxicity. *J Forensic Leg Med*. 2013;20(8):1122-1125. https://doi.org/10.1016/j.jflm.2013.09.002.
176. Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics. A neuropathological study with clinical correlations. *J Neurol Sci*. 1982;56(2-3):233-248. https://doi.org/110.1016/0022-510x(82)90145-9.
177. Harding AJ, Wong A, Svoboda M, Kril JJ, Halliday GM. Chronic alcohol consumption does not cause hippocampal neuron loss in humans. *Hippocampus*. 1997;7(1):78-87. https://doi.org/10.1002/(SICI)1098-1063(1997)7:1<78::AID-HIPO8>3.0.CO;2-3.
178. Harper C, Dixon G, Sheedy D, Garrick T. Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales Tissue Resource Centre. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(6):951-961. https://doi.org/10.1016/S0278-5846(03)00155-6.
179. Baker KG, Halliday GM, Kril JJ, Harper CG. Chronic alcoholics without Wernicke-Korsakoff syndrome or cirrhosis do not lose serotonergic neurons in the dorsal raphe nucleus. *Alcohol Clin Exp Res*. 1996;20(1):61-66. https://doi.org/10.1111/j.1530-0277.1996.tb01045.x.
180. Halliday G, Ellis J, Heard R, Caine D, Harper C. Brainstem serotonergic neurons in chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. *J Neuropathol Exp Neurol*. 1993;52(6):567-579. https://doi.org/10.1097/00005072-199311000-00003.
181. Thompson PM, Cruz DA, Olukotun DY, Delgado PL. Serotonin receptor, SERT mRNA and correlations with symptoms in males with alcohol dependence and suicide. *Acta Psychiatr Scand*. 2012;126(3):165-174. https://doi.org/10.1111/j.1600-0447.2011.01816.x.
182. Fabricius K, Pakkenberg H, Pakkenberg B. No changes in neocortical cell volumes or glial cell numbers in chronic alcoholic subjects compared to control subjects. *Alcohol Alcohol*. 2007;42(5):400-406. https://doi.org/10.1093/alcalc/agm007.
183. Ferrer I, Fábregues I, Rairiz J, Galofré E. Decreased numbers of dendritic spines on cortical pyramidal neurons in human chronic alcoholism. *Neurosci Lett*. 1986;69(1):115-119. https://doi.org/10.1016/0304-3940(86)90425-8.
184. Skuja S, Groma V, Smane L. Alcoholism and cellular vulnerability in different brain regions. *Ultrastruct Pathol*. 2012;36(1):40-47. https://doi.org/10.3109/01913123.2011.629770.
185. de la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch Neurol*. 1988;45(9):990-992. https://doi.org/10.1001/archneur.1988.00520330076013.
186. Phillips SC, Harper CG, Kril J. A quantitative histological study of the cerebellar vermis in alcoholic patients. *Brain*. 1987;110 (Pt 2):301-314.
187. McCorkindale AN, Sheedy D, Kril JJ, Sutherland GT. The effects of chronic smoking on the pathology of alcohol-related brain damage. *Alcohol*. 2016;53:35-44. https://doi.org/10.1016/j.alcohol.2016.04.002.
188. de la Monte SM, Kay J, Yalcin EB, Kril JJ, Sheedy D, Sutherland GT. Imaging mass spectrometry of frontal white matter lipid changes in human alcoholics. *Alcohol*. 2018;67:51-63. https://doi.org/10.1016/j.alcohol.2017.08.004.
189. Freund G, Ballinger WE Jr. Alzheimer's disease and alcoholism: Possible interactions. *Alcohol*. 1992;9(3):233-240. https://doi.org/10.1016/0741-8329(92)90059-j.
190. Kok EH, Karppinen TT, Luoto T, Alafuzoff I, Karhunen PJ. Beer drinking associates with lower burden of amyloid beta aggregation in the brain: Helsinki Sudden Death Series. *Alcohol Clin Exp Res*. 2016;40(7):1473-1478. https://doi.org/10.1111/acer.13102.
191. Wardzala C, Murchison C, Loftis JM, et al. Sex differences in the association of alcohol with cognitive decline and brain pathology in a cohort of octogenarians. *Psychopharmacology (Berl)*. 2018;235(3):761-770. https://doi.org/10.1007/s00213-017-4791-6.
192. Cullen KM, Halliday GM. Neurofibrillary tangles in chronic alcoholics. *Neuropathol Appl Neurobiol*. 1995;21(4):312-318. https://doi.org/10.1111/j.1365-2990.1995.tb01065.x.
193. Aho L, Karkola K, Juusela J, Alafuzoff I. Heavy alcohol consumption and neuropathological lesions: A post-mortem human study. *J Neurosci Res*. 2009;87(12):2786-2792. https://doi.org/10.1002/jnr.22091.
194. Iso H, Baba S, Mannami T, et al. Alcohol consumption and risk of stroke among middle-aged men: The JPHC Study Cohort I. *Stroke*. 2004;35(5):1124-1129. https://doi.org/10.1161/01.Str.0000124459.33597.00.
195. Sullivan EV, Pfefferbaum A. Neuroradiological characterization of normal adult ageing. *Br J Radiol*. 2007;80 Spec No 2:S99-108. https://doi.org/10.1259/bjr/22893432.
196. de Mélo Silva Júnior ML, Diniz PRB, de Souza Vilanova MV, Basto GPT, Valença MM. Brain ventricles, CSF and cognition: A narrative review. *Psychogeriatrics*. 2022;22(4):544-552. https://doi.org/10.1111/psyg.12839.
197. Hidaka Y, Hashimoto M, Suehiro T, et al. Impact of age on the cerebrospinal fluid spaces: High-convexity and medial subarachnoid spaces decrease with age. *Fluids Barriers CNS*. 2022;19(1):82. https://doi.org/10.1186/s12987-022-00381-5.
198. Leong RLF, Lo JC, Sim SKY, et al. Longitudinal brain structure and cognitive changes over 8 years in an East Asian cohort. *Neuroimage*. 2017;147:852-860. https://doi.org/10.1016/j.neuroimage.2016.10.016.

199. Gómez-Ramírez J, Fernández-Blázquez MA, González-Rosa JJ. A causal analysis of the effect of age and sex differences on brain atrophy in the elderly brain. *Life (Basel)*. 2022;12(10):1586. https://doi.org/10.3390/life12101586.
200. Woodworth DC, Scambray KA, Corrada MM, Kawas CH, Sajjadi SA. Neuroimaging in the oldest-old: A review of the literature. *J Alzheimers Dis*. 2021;82(1):129-147. https://doi.org/10.3233/jad-201578.
201. Pfefferbaum A, Rohlfing T, Rosenbloom MJ, Chu W, Colrain IM, Sullivan EV. Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. *Neuroimage*. 2013;65:176-193. https://doi.org/10.1016/j.neuroimage.2012.10.008.
202. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry*. 1998;55(10):905-912. https://doi.org/10.1001/archpsyc.55.10.905.
203. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *J Neurosci*. 2003;23(8):3295-3301. https://doi.org/10.1523/jneurosci.23-08-03295.2003.
204. Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: Replicability of regional differences in volume. *Neurobiol Aging*. 2004;25(3):377-396. https://doi.org/10.1016/S0197-4580(03)00118-0.
205. Zimmerman ME, Brickman AM, Paul RH, et al. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am J Geriatr Psychiatry*. 2006;14(10):823-833. https://doi.org/10.1097/01.JGP.0000238502.40963.ac.
206. Hogstrom LJ, Westlye LT, Walhovd KB, Fjell AM. The structure of the cerebral cortex across adult life: Age-related patterns of surface area, thickness, and gyrification. *Cereb Cortex*. 2013;23(11):2521-2530. https://doi.org/10.1093/cercor/bhs231.
207. Pfefferbaum A, Zhao Q, Pohl KM, Sassoon SA, Zahr NM, Sullivan EV. Age-accelerated increase of white matter hyperintensity volumes is exacerbated by heavy alcohol use in people living with HIV. *Biol Psychiatry*. 2024;95(3):231-244. https://doi.org/10.1016/j.biopsych.2023.07.023.
208. Fama R, Sullivan EV. Thalamic structures and associated cognitive functions: Relations with age and aging. *Neurosci Biobehav Rev*. 2015;54:29-37. https://doi.org/10.1016/j.neubiorev.2015.03.008.
209. Ramanoël S, Durteste M, Perot V, Habas C, Arleo A. An appraisal of the role of the neocerebellum for spatial navigation in healthy aging. *Cerebellum*. 2023;22(2):235-239. https://doi.org/10.1007/s12311-022-01389-1.
210. Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A. Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology*. 2000;14(3):341-352. https://doi.org/10.1037//0894-4105.14.3.341.
211. Hicks TH, Ballard HK, Sang H, Bernard JA. Age-volume associations in cerebellar lobules by sex and reproductive stage. *Brain Struct Funct*. 2022;227(7):2439-2455. https://doi.org/10.1007/s00429-022-02535-5.
212. Raz N, Rodrigue KM. Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev*. 2006;30(6):730-748. https://doi.org/10.1016/j.neubiorev.2006.07.001.
213. Yeatman JD, Wandell BA, Mezer AA. Lifespan maturation and degeneration of human brain white matter. *Nat Commun*. 2014;5:4932. https://doi.org/10.1038/ncomms5932.
214. Coupé P, Catheline G, Lanuza E, Manjón JV; Alzheimer's Disease Neuroimaging Initiative. Towards a unified analysis of brain maturation and aging across the entire lifespan: A MRI analysis. *Hum Brain Mapp*. 2017;38(11):5501-5518. https://doi.org/10.1002/hbm.23743.
215. Dey AK, Stamenova V, Bacopulos A, et al. Cognitive heterogeneity among community-dwelling older adults with cerebral small vessel disease. *Neurobiol Aging*. 2019;77:183-193. https://doi.org/10.1016/j.neurobiolaging.2018.12.011.
216. Grosset L, Jouvent E. Cerebral small-vessel diseases: A look back from 1991 to today. *Cerebrovasc Dis*. 2022;51(2):131-137. https://doi.org/10.1159/000522213.
217. Habes M, Erus G, Toledo JB, et al. White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain*. 2016;139(Pt 4):1164-1179. https://doi.org/10.1093/brain/aww008.
218. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J Am Heart Assoc*. 2015;4(6):001140. https://doi.org/10.1161/JAHA.114.001140.
219. Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn Reson Med*. 2000;44(2):259-268. https://doi.org/10.1002/1522-2594(200008)44:2<259::aid-mrm13>3.0.co;2-6.
220. Sullivan EV, Adalsteinsson E, Sood R, et al. Longitudinal brain magnetic resonance imaging study of the alcohol-preferring rat. Part I: Adult brain growth. *Alcohol Clin Exp Res*. 2006;30(7):1234-1247. https://doi.org/10.1111/j.1530-0277.2006.00145.x.
221. Pietrasik W, Cribben I, Olsen F, Malykhin N. Diffusion tensor imaging of superficial prefrontal white matter in healthy aging. *Brain Res*. 2023;1799:148152. https://doi.org/10.1016/j.brainres.2022.148152.
222. Kok CY, Lock C, Ang TY, Keong NC. Modeling the properties of white matter tracts using diffusion tensor imaging to characterize patterns of injury in aging and neurodegenerative disease. *Front Aging Neurosci*. 2022;14:787516. https://doi.org/10.3389/fnagi.2022.787516.
223. Pfefferbaum A, Rosenbloom MJ, Sassoon SA, et al. Regional brain structural dysmorphology in human immunodeficiency virus infection: Effects of acquired immune deficiency syndrome, alcoholism, and age. *Biol Psychiatry*. 2012;72(5):361-370. https://doi.org/10.1016/j.biopsych.2012.02.018.
224. Makris N, Oscar-Berman M, Jaffin SK, et al. Decreased volume of the brain reward system in alcoholism. *Biol Psychiatry*. 2008;64(3):192-202. https://doi.org/10.1016/j.biopsych.2008.01.018.
225. Muller AM, Meyerhoff DJ. Frontocerebellar gray matter plasticity in alcohol use disorder linked to abstinence. *Neuroimage Clin*. 2021;32:102788. https://doi.org/10.1016/j.nicl.2021.102788.
226. Sullivan EV. Compromised pontocerebellar and cerebellothalamocortical systems: Speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. *Alcohol Clin Exp Res*. 2003;27(9):1409-1419. https://doi.org/10.1097/01.ALC.0000085586.91726.46.
227. Sullivan EV, Zahr NM, Sassoon SA, et al. The role of aging, drug dependence, and hepatitis C comorbidity in alcoholism cortical compromise. *JAMA Psychiatry*. 2018; 75(5):474-483. https://doi.org/10.1001/jamapsychiatry.2018.0021.
228. Zahr NM, Sullivan EV, Pohl KM, Pfefferbaum A. Age differences in brain structural and metabolic responses to binge ethanol exposure in Fisher 344 rats. *Neuropsychopharmacology*. 2021;46(2):368-379. https://doi.org/10.1038/s41386-020-0744-6.
229. Le Berre AP, Pitel AL, Chanraud S, et al. Chronic alcohol consumption and its effect on nodes of frontocerebellar and limbic circuitry: Comparison of effects in France and the United States. *Hum Brain Mapp*. 2014;35(9):4635-4653. https://doi.org/10.1002/hbm.22500.
230. Sullivan EV, Pfefferbaum A. Neuroimaging of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol*. 2009;44(2):155-165. https://doi.org/10.1093/alcalc/agn103.

231. Durazzo TC, Tosun D, Buckley S, et al. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: Relationships to relapse and extended abstinence. *Alcohol Clin Exp Res*. 2011;35(6):1187-1200. https://doi.org/10.1111/j.1530-0277.2011.01452.x.
232. Zahr NM, Pohl KM, Saranathan M, Sullivan EV, Pfefferbaum A. Hippocampal subfield CA2+3 exhibits accelerated aging in alcohol use disorder: A preliminary study. *Neuroimage Clin*. 2019;22:101764. https://doi.org/10.1016/j.nicl.2019.101764.
233. Sawyer KS, Adra N, Salz DM, et al. Hippocampal subfield volumes in abstinent men and women with a history of alcohol use disorder. *PLoS One*. 2020;15(8):e0236641. https://doi.org/10.1371/journal.pone.0236641.
234. Sullivan EV, Marsh L, Pfefferbaum A. Preservation of hippocampal volume throughout adulthood in healthy men and women. *Neurobiol Aging*. 2005;26(7):1093-1098. https://doi.org/10.1016/j.neurobiolaging.2004.09.015.
235. Daviet R, Aydogan G, Jagannathan K, et al. Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. *Nat Commun*. 2022;13(1):1175. https://doi.org/10.1038/s41467-022-28735-5.
236. Pfefferbaum A, Lim KO, Zipursky RB, et al. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: A quantitative MRI study. *Alcohol Clin Exp Res*. 1992;16(6):1078-1089. https://doi.org/10.1111/j.1530-0277.1992.tb00702.x.
237. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol Clin Exp Res*. 1997;21(3):521-529. https://doi.org/0.1111/j.1530-0277.1997.tb03798.x.
238. Angebrandt A, Abulseoud OA, Kisner M, et al. Dose-dependent relationship between social drinking and brain aging. *Neurobiol Aging*. 2022;111:71-81. https://doi.org/10.1016/j.neurobiolaging.2021.11.008.
239. Pfefferbaum A, Zahr NM, Sassoon SA, Kwon D, Pohl KM, Sullivan EV. Accelerated and premature aging characterizing regional cortical volume loss in human immunodeficiency virus infection: Contributions from alcohol, substance use, and hepatitis C coinfection. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(10):844-859. https://doi.org/10.1016/j.bpsc.2018.06.006.
240. van Eijk J, Demirakca T, Frischknecht U, Hermann D, Mann K, Ende G. Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. *Alcohol Clin Exp Res*. 2013;37(1):67-74. https://doi.org/10.1111/j.1530-0277.2012.01853.x.
241. Durazzo TC, Mon A, Gazdzinski S, Yeh PH, Meyerhoff DJ. Serial longitudinal magnetic resonance imaging data indicate non-linear regional gray matter volume recovery in abstinent alcohol-dependent individuals. *Addict Biol*. 2015;20(5):956-967. https://doi.org/10.1111/adb.12180.
242. Zou X, Durazzo TC, Meyerhoff DJ. Regional brain volume changes in alcohol-dependent individuals during short-term and long-term abstinence. *Alcohol Clin Exp Res*. 2018;42(6):1062-1072. https://doi.org/10.1111/acer.13757.
243. Shear PK, Jernigan TL, Butters N. Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcohol Clin Exp Res*. 1994;18(1):172-176. https://doi.org/10.1111/j.1530-0277.1994.tb00899.x.
244. Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcohol Clin Exp Res*. 1995;19(5):1177-1191. https://doi.org/10.1111/j.1530-0277.1995.tb01598.x.
245. Segobin SH, Chetelat G, Le Berre AP, et al. Relationship between brain volumetric changes and interim drinking at six months in alcohol-dependent patients. *Alcohol Clin Exp Res*. 2014;38(3):739-748. https://doi.org/10.1111/acer.12300.
246. Durazzo TC, Meyerhoff DJ. Changes of frontal cortical subregion volumes in alcohol dependent individuals during early abstinence: Associations with treatment outcome. *Brain Imaging Behav*. 2020;14(5):1588-1599. https://doi.org/10.1007/s11682-019-00089-5.
247. Meyerhoff DJ, Durazzo TC. Not all is lost for relapsers: Relapsers with low WHO risk drinking levels and complete abstainers have comparable regional gray matter volumes. *Alcohol Clin Exp Res*. 2020;44(7):1479-1487. https://doi.org/10.1111/acer.14377.
248. Kuhn S, Charlet K, Schubert F, et al. Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. *JAMA Psychiatry*. 2014;71(7):806-811. https://doi.org/10.1001/jamapsychiatry.2014.352.
249. Lee J, Im S-J, Lee S-G, et al. Volume of hippocampal subfields in patients with alcohol dependence. *Psychiatry Res Neuroimaging*. 2016;258:16-22. https://doi.org/10.1016/j.pscychresns.2016.10.009.
250. Mufson EJ, Ikonomovic MD, Counts SE, et al. Molecular and cellular pathophysiology of preclinical Alzheimer's disease. *Behav Brain Res*. 2016;311:54-69. https://doi.org/10.1016/j.bbr.2016.05.030.
251. Alcalà-Vida R, Awada A, Boutillier A-L, Merienne K. Epigenetic mechanisms underlying enhancer modulation of neuronal identity, neuronal activity and neurodegeneration. *Neurobiol Dis*. 2021;147:105155. https://doi.org/10.1016/j.nbd.2020.105155.
252. McCormick LM, Buchanan JR, Onwuameze OE, Pierson RK, Paradiso S. Beyond alcoholism: Wernicke-Korsakoff syndrome in patients with psychiatric disorders. *Cogn Behav Neurol*. 2011;24(4):209-216. https://doi.org/10.1097/WNN.0b013e31823f90c4.
253. Silva AR, Almeida-Xavier S, Lopes M, Soares-Fernandes JP, Sousa F, Varanda S. Is there a time window for MRI in Wernicke encephalopathy - a decade of experience from a tertiary hospital. *Neurol Sci*. 2023;44(2):703-708. https://doi.org/10.1007/s10072-022-06477-y.
254. Zuccoli G. The importance of knowing the typical and atypical imaging findings of Wernicke encephalopathy. *Acta Neurol Belg*. 2021;121(5):1399-1400. https://doi.org/10.1007/s13760-020-01482-4.
255. Pitel A-L, Chételat G, Le Berre AP, Desgranges B, Eustache F, Beaunieux H. Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated alcoholism. *Neurology*. 2012;78(17):1330-1333. https://doi.org/10.1212/WNL.0b013e318251834e.
256. Grodin EN, Lin H, Durkee CA, Hommer DW, Momenan R. Deficits in cortical, diencephalic and midbrain gray matter in alcoholism measured by VBM: Effects of co-morbid substance abuse. *Neuroimage Clin*. 2013;2:469-476. https://doi.org/10.1016/j.nicl.2013.03.013.
257. Charness ME, DeLaPaz RL. Mamillary body atrophy in Wernicke's encephalopathy: Antemortem identification using magnetic resonance imaging. *Ann Neurol*. 1987;22(5):595-600. https://doi.org/10.1002/ana.410220506.
258. Sullivan EV, Marsh L. Hippocampal volume deficits in alcoholic Korsakoff's syndrome. *Neurology*. 2003;61(12):1716-1719. https://doi.org/10.1212/01.wnl.0000098940.31882.bb.
259. Segobin S, Laniepce A, Ritz L, et al. Dissociating thalamic alterations in alcohol use disorder defines specificity of Korsakoff's syndrome. *Brain*. 2019;142(5):1458-1470. https://doi.org/10.1093/brain/awz056.
260. Fjell AM, Westlye LT, Grydeland H, et al. Critical ages in the life course of the adult brain: Nonlinear subcortical aging. *Neurobiol Aging*. 2013;34(10):2239-2247. https://doi.org/10.1016/j.neurobiolaging.2013.04.006.
261. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. *Alcohol Clin Exp Res*. 1995;19(1):110-122. https://doi.org/0.1111/j.1530-0277.1995.tb01478.x.

262. Callen DJ, Black SE, Gao F, Caldwell CB, Szalai JP. Beyond the hippocampus: MRI volumetry confirms widespread limbic atrophy in AD. *Neurology*. 2001;57(9):1669-1674. https://doi.org/10.1212/wnl.57.9.1669.
263. Ben Ahmed O, Benois-Pineau J, Allard M, Ben Amar C, Catheline G. Classification of Alzheimer's disease subjects from MRI using hippocampal visual features. *Multimedia Tools and Applications*. 2015;74(4):1249-1266. https://doi.org/10.1007/s11042-014-2123-y.
264. Khan W, Westman E, Jones N, et al. Automated hippocampal subfield measures as predictors of conversion from mild cognitive impairment to Alzheimer's disease in two independent cohorts. *Brain Topogr*. 2015;28(5):746-759. https://doi.org/10.1007/s10548-014-0415-1.
265. Li X, Li D, Li Q, et al. Hippocampal subfield volumetry in patients with subcortical vascular mild cognitive impairment. *Sci Rep*. 2016;6:20873. https://doi.org/10.1038/srep20873.
266. Shim G, Choi KY, Kim D, et al. Predicting neurocognitive function with hippocampal volumes and DTI metrics in patients with Alzheimer's dementia and mild cognitive impairment. *Brain Behav*. 2017;7(9):e00766. https://doi.org/10.1002/brb3.766.
267. Mak E, Su L, Williams GB, et al. Differential atrophy of hippocampal subfields: A comparative study of dementia with Lewy bodies and Alzheimer disease. *Am J Geriatr Psychiatry*. 2016;24(2):136-143. https://doi.org/10.1016/j.jagp.2015.06.006.
268. Cavedo E, Boccardi M, Ganzola R, et al. Local amygdala structural differences with 3T MRI in patients with Alzheimer disease. *Neurology*. 2011;76(8):727-733. https://doi.org/10.1212/WNL.0b013e31820d62d9.
269. Bron EE, Smits M, van der Flier WM, et al. Standardized evaluation of algorithms for computer-aided diagnosis of dementia based on structural MRI: The CADDementia challenge. *Neuroimage*. 2015;111:562-579. https://doi.org/10.1016/j.neuroimage.2015.01.048.
270. Baskar D, Jayanthi VS, Jayanthi AN. An efficient classification approach for detection of Alzheimer's disease from biomedical imaging modalities. *Multimed Tools Appl*. 2019;78:12883-12915. https://doi.org/10.1007/s11042-018-6287-8.
271. Henson RN, Campbell KL, Davis SW, et al. Multiple determinants of lifespan memory differences. *Sci Rep*. 2016;6:32527. https://doi.org/10.1038/srep32527.
272. Yu J, Lam CLM, Lee TMC. White matter microstructural abnormalities in amnestic mild cognitive impairment: A meta-analysis of whole-brain and ROI-based studies. *Neurosci Biobehav Rev*. 2017;83:405-416. https://doi.org/10.1016/j.neubiorev.2017.10.026.
273. Chhatwal JP, Schultz AP, Marshall GA, et al. Temporal T807 binding correlates with CSF tau and phospho-tau in normal elderly. *Neurology*. 2016;87(9):920-926. https://doi.org/10.1212/WNL.0000000000003050.
274. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011;32(7):1207-1218. https://doi.org/10.1016/j.neurobiolaging.2009.07.002.
275. Villain N, Chételat G, Grassiot B, et al. Regional dynamics of amyloid-β deposition in healthy elderly, mild cognitive impairment and Alzheimer's disease: A voxelwise PiB–PET longitudinal study. *Brain*. 2012;135(Pt 7):2126-2139. https://doi.org/10.1093/brain/aws125.
276. Silverberg N, Elliott C, Ryan L, Masliah E, Hodes R. NIA commentary on the NIA-AA Research Framework: Towards a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):576-578. https://doi.org/10.1016/j.jalz.2018.03.004.
277. Inoue Y, Shue F, Bu G, Kanekiyo T. Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. *Mol Neurodegener*. 2023;18(1):46. https://doi.org/10.1186/s13024-023-00640-5.
278. Li X, Su F, Yuan Q, Chen Y, Liu CY, Fan Y. Advances in differential diagnosis of cerebrovascular diseases in magnetic resonance imaging: A narrative review. *Quant Imaging Med Surg*. 2023;13(4):2712-2734. https://doi.org/10.21037/qims-22-750.
279. Prajjwal P, Marsool MDM, Inban P, et al. Vascular dementia subtypes, pathophysiology, genetics, neuroimaging, biomarkers, and treatment updates along with its association with Alzheimer's dementia and diabetes mellitus. *Dis Mon*. 2023;69(5):101557. https://doi.org/10.1016/j.disamonth.2023.101557.
280. Raji CA, Benzinger TLS. The value of neuroimaging in dementia diagnosis. *Continuum (Minneap Minn)*. 2022;28(3):800-821. https://doi.org/10.1212/con.0000000000001133.
281. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: Mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696. https://doi.org/10.1016/s1474-4422(19)30079-1.
282. Cai Y, Song W, Li J, et al. The landscape of aging. *Sci China Life Sci*. 2022;65(12):2354-2454. https://doi.org/10.1007/s11427-022-2161-3.
283. Mahammedi A, Wang LL, Williamson BJ, et al. Small vessel disease, a marker of brain health: What the radiologist needs to know. *AJNR Am J Neuroradiol*. 2022;43(5):650-660. https://doi.org/10.3174/ajnr.A7302.
284. Chen Y, Wang X, Guan L, Wang Y. Role of white matter hyperintensities and related risk factors in vascular cognitive impairment: A review. *Biomolecules*. 2021;11(8):1102. https://doi.org/10.3390/biom11081102.
285. Hu HY, Ou YN, Shen XN, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. *Neurosci Biobehav Rev*. 2021;120:16-27. https://doi.org/10.1016/j.neubiorev.2020.11.007.
286. Twait EL, Min B, Beran M, Vonk JMJ, Geerlings MI. The cross-sectional association between amyloid burden and white matter hyperintensities in older adults without cognitive impairment: A systematic review and meta-analysis. *Ageing Res Rev*. 2023;88:101952. https://doi.org/10.1016/j.arr.2023.101952.
287. Eloyan A, Thangarajah M, An N, et al. White matter hyperintensities are higher among early-onset Alzheimer's disease participants than their cognitively normal and early-onset nonAD peers: Longitudinal Early-onset Alzheimer's Disease Study (LEADS). *Alzheimers Dement*. 2023;19 (suppl 9):S89-S97. https://doi.org/10.1002/alz.13402.
288. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging*. 1995;16(4):591-606. https://doi.org/10.1016/0197-4580(95)00074-o.
289. Suzuki H, Venkataraman AV, Bai W, et al. Associations of regional brain structural differences with aging, modifiable risk factors for dementia, and cognitive performance. *JAMA Netw Open*. 2019;2(12): e1917257. https://doi.org/10.1001/jamanetworkopen.2019.17257.
290. Zhornitsky S, Chaudhary S, Le TM, et al. Cognitive dysfunction and cerebral volumetric deficits in individuals with Alzheimer's disease, alcohol use disorder, and dual diagnosis. *Psychiatry Res Neuroimaging*. 2021;317:111380. https://doi.org/10.1016/j.pscychresns.2021.111380.
291. Flanigan MR, Royse SK, Cenkner DP, et al. Imaging beta-amyloid (Aβ) burden in the brains of middle-aged individuals with alcohol-use disorders: A [^{11}C]PiB PET study. *Transl Psychiatry*. 2021;11(1):257. https://doi.org/10.1038/s41398-021-01374-y.
292. Koch M, Costanzo S, Fitzpatrick AL, et al. Alcohol consumption, brain amyloid-β deposition, and brain structural integrity among older adults free of dementia. *J Alzheimers Dis*. 2020;74(2):509-519. https://doi.org/10.3233/jad-190834.

293. Mendes A, Tezenas du Montcel S, Levy M, et al. Multimorbidity is associated with preclinical Alzheimer's disease neuroimaging biomarkers. *Dement Geriatr Cogn Disord*. 2018;45(5-6):272-281. https://doi.org/10.1159/000489007.
294. Kim JW, Byun MS, Yi D, et al. Association of moderate alcohol intake with in vivo amyloid-beta deposition in human brain: A cross-sectional study. *PLoS Med*. 2020;17(2):e1003022. https://doi.org/10.1371/journal.pmed.1003022.
295. Sullivan EV, Rohlfing T, Pfefferbaum A. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Dev Neuropsychol*. 2010;35(3): 233-256. https://doi.org/10.1080/87565641003689556.
296. Fjell AM, Walhovd KB. Structural brain changes in aging: Courses, causes and cognitive consequences. *Rev Neurosci*. 2010;21(3): 187-221. https://doi.org/10.1515/revneuro.2010.21.3.187.
297. Kohama SG, Rosene DL, Sherman LS. Age-related changes in human and non-human primate white matter: From myelination disturbances to cognitive decline. *Age (Dordr)*. 2012;34(5): 1093-1110. https://doi.org/10.1007/s11357-011-9357-7.
298. MacDonald ME, Pike GB. MRI of healthy brain aging: A review. *NMR Biomed*. 2021;34(9):e4564. https://doi.org/10.1002/nbm.4564.
299. Pfefferbaum A, Rosenbloom MJ, Chu W, et al. White matter microstructural recovery with abstinence and decline with relapse in alcohol dependence interacts with normal ageing: A controlled longitudinal DTI study. *Lancet Psychiatry*. 2014;1(3):202-212. https://doi.org/10.1016/S2215-0366(14)70301-3.
300. Sharma B, Beaudin AE, Cox E, et al. Brain iron content in cerebral amyloid angiopathy using quantitative susceptibility mapping. *Front Neurosci*. 2023;17:1139988. https://doi.org/10.3389/fnins.2023.1139988.
301. de Souza ID, Queiroz MEC. Advances in sample preparation and HPLC-MS/MS methods for determining amyloid-β peptide in biological samples: A review. *Anal Bioanal Chem*. 2023;415(18):4003-4021. https://doi.org/10.1007/s00216-023-04631-9.
302. Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: Towards implementation in clinical practice and trials. *Lancet Neurol*. 2022;21(8):726-734. https://doi.org/10.1016/s1474-4422(22)00168-5.
303. Zetterberg H, Pedersen M, Lind K, et al. Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. *J Alzheimers Dis*. 2007;12(3):255-260. https://doi.org/10.3233/jad-2007-12307.
304. Buongiorno M, Antonelli F, Compta Y, et al. Cross-sectional and longitudinal cognitive correlates of FDDNP PET and CSF amyloid-β and tau in Parkinson's disease1. *J Alzheimers Dis*. 2017;55(3):1261-1272. https://doi.org/10.3233/jad-160698.
305. Wisch JK, Gordon BA, Boerwinkle AH, et al. Predicting continuous amyloid PET values with CSF and plasma Aβ42/Aβ40. *Alzheimers Dement (Amst)*. 2023;15(1):e12405. https://doi.org/10.1002/dad2.12405.
306. de Leon MJ, Pirraglia E, Osorio RS, et al. The nonlinear relationship between cerebrospinal fluid Aβ42 and tau in preclinical Alzheimer's disease. *PLoS One*. 2018;13(2):e0191240. https://doi.org/10.1371/journal.pone.0191240.
307. Li QX, Villemagne VL, Doecke JD, et al. Alzheimer's disease normative cerebrospinal fluid biomarkers validated in PET amyloid-β characterized subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. *J Alzheimers Dis*. 2015;48(1):175-187. https://doi.org/10.3233/jad-150247.
308. Struyfs H, Van Broeck B, Timmers M, et al. Diagnostic accuracy of cerebrospinal fluid amyloid-β isoforms for early and differential dementia diagnosis. *J Alzheimers Dis*. 2015;45(3):813-822. https://doi.org/10.3233/jad-141986.
309. Behzad M, Zirak N, Madani GH, et al. CSF-targeted proteomics indicate amyloid-beta ratios in patients with Alzheimer's dementia spectrum. *Int J Alzheimers Dis*. 2023;2023:5336273. https://doi.org/10.1155/2023/5336273.
310. Kokkinou M, Beishon LC, Smailagic N, et al. Plasma and cerebrospinal fluid ABeta42 for the differential diagnosis of Alzheimer's disease dementia in participants diagnosed with any dementia subtype in a specialist care setting. *Cochrane Database Syst Rev*. 2021;2(2):CD010945. https://doi.org/10.1002/14651858.CD010945.pub2.
311. Hermann P, Haller P, Goebel S, et al. Total and phosphorylated cerebrospinal fluid tau in the differential diagnosis of sporadic Creutzfeldt-Jakob disease and rapidly progressive Alzheimer's disease. *Viruses*. 2022;14(2):276. https://doi.org/10.3390/v14020276.
312. Schaeffer MJ, Callahan BL. Investigating the association between verbal forgetting and pathological markers of Alzheimer's and Lewy body diseases. *J Alzheimers Dis*. 2019;70(3):877-887. https://doi.org/10.3233/jad-180962.
313. Rosenberg A, Solomon A, Jelic V, Hagman G, Bogdanovic N, Kivipelto M. Progression to dementia in memory clinic patients with mild cognitive impairment and normal β-amyloid. *Alzheimers Res Ther*. 2019;11(1):99. https://doi.org/10.1186/s13195-019-0557-1.
314. Vogelgsang J, Wedekind D, Bouter C, Klafki HW, Wiltfang J. Reproducibility of Alzheimer's disease cerebrospinal fluid-biomarker measurements under clinical routine conditions. *J Alzheimers Dis*. 2018;62(1):203-212. https://doi.org/10.3233/jad-170793.
315. Constantinides VC, Paraskevas GP, Boufidou F, et al. CSF Aβ42 and Aβ42/Aβ40 ratio in Alzheimer's disease and frontotemporal dementias. *Diagnostics (Basel)*. 2023;13(4):783. https://doi.org/10.3390/diagnostics13040783.
316. Matsushita S, Miyakawa T, Maesato H, et al. Elevated cerebrospinal fluid tau protein levels in Wernicke's encephalopathy. *Alcohol Clin Exp Res*. 2008;32(6):1091-1095. https://doi.org/10.1111/j.1530-0277.2008.00671.x.
317. Azuar J, Bouaziz-Amar E, Cognat E, et al. Cerebrospinal fluid biomarkers in patients with alcohol use disorder and persistent cognitive impairment. *Alcohol Clin Exp Res*. 2021;45(3):561-565. https://doi.org/10.1111/acer.14554.
318. Kučikienė D, Costa AS, Banning LCP, et al. The role of vascular risk factors in biomarker-based AT(N) groups: A German-Dutch memory clinic study. *J Alzheimers Dis*. 2022;87(1):185-195. https://doi.org/10.3233/jad-215391.
319. Kapaki E, Liappas I, Paraskevas GP, Theotoka I, Rabavilas A. The diagnostic value of tau protein, beta-amyloid (1-42) and their ratio for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. *Int J Geriatr Psychiatry*. 2005;20(8):722-729. https://doi.org/10.1002/gps.1351.
320. Hampel H, Hu Y, Cummings J, et al. Blood-based biomarkers for Alzheimer's disease: Current state and future use in a transformed global healthcare landscape. *Neuron*. 2023;111(18):2781-2799. https://doi.org/10.1016/j.neuron.2023.05.017.
321. Fu J, Lai X, Huang Y, et al. Meta-analysis and systematic review of peripheral platelet-associated biomarkers to explore the pathophysiology of Alzheimer's disease. *BMC Neurol*. 2023;23(1):66. https://doi.org/10.1186/s12883-023-03099-5.
322. Delaby C, Alcolea D, Hirtz C, et al. Blood amyloid and tau biomarkers as predictors of cerebrospinal fluid profiles. *J Neural Transm (Vienna)*. 2022;129(2):231-237. https://doi.org/10.1007/s00702-022-02474-9.
323. Janelidze S, Palmqvist S, Leuzy A, et al. Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau. *Alzheimers Dement*. 2022;18(2):283-293. https://doi.org/10.1002/alz.12395.
324. Burnham SC, Fandos N, Fowler C, et al. Longitudinal evaluation of the natural history of amyloid-β in plasma and brain. *Brain Commun*. 2020;2(1):fcaa041. https://doi.org/10.1093/braincomms/fcaa041.

325. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: Findings from a multi cohort validity analysis. *Mol Neurodegener*. 2021;16(1):30. https://doi.org/10.1186/s13024-021-00451-6.
326. Brizzee KR, Sherwood N, Timiras PS. A comparison of cell populations at various depth levels in cerebral cortex of young adult and aged Long-Evans rats. *J Gerontol*. 1968;23(3):289-297. https://doi.org/10.1093/geronj/23.3.289.
327. Diamond MC, Johnson RE, Ingham CA. Morphological changes in the young, adult and aging rate cerebral cortex, hippocampus, and diencephalon. *Behav Biol*. 1975;14(2):163-174. https://doi.org/10.1016/s0091-6773(75)90161-3.
328. Pfefferbaum A, Zahr NM, Mayer D, et al. Ventricular expansion in wild-type Wistar rats after alcohol exposure by vapor chamber. *Alcohol Clin Exp Res*. 2008;32(8):1459-1467. https://doi.org/10.1111/j.1530-0277.2008.00721.x.
329. Pfefferbaum A, Adalsteinsson E, Sood R, et al. Longitudinal brain magnetic resonance imaging study of the alcohol-preferring rat. Part II: Effects of voluntary chronic alcohol consumption. *Alcohol Clin Exp Res*. 2006;30(7):1248-1261. https://doi.org/10.1111/j.1530-0277.2006.00146.x.
330. Zahr NM, Mayer D, Rohlfing T, et al. Rat strain differences in brain structure and neurochemistry in response to binge alcohol. Research Support, N.I.H., Extramural. *Psychopharmacology (Berl)*. 2014;231(2):429-445. https://doi.org/10.1007/s00213-013-3253-z.
331. Zahr NM, Lenart AM, Karpf JA, et al. Multi-modal imaging reveals differential brain volumetric, biochemical, and white matter fiber responsivity to repeated intermittent ethanol vapor exposure in male and female rats. *Neuropharmacology*. 2020;170:108066. https://doi.org/10.1016/j.neuropharm.2020.108066.
332. French SW. Intragastric ethanol infusion model for cellular and molecular studies of alcoholic liver disease. *J Biomed Sci*. 2001;8(1):20-27. https://doi.org/10.1007/BF02255967.
333. Fernandez-Lizarbe S, Pascual M, Guerri C. Critical role of TLR4 response in the activation of microglia induced by ethanol. *J Immunol*. 2009;183(7):4733-4744. https://doi.org/10.4049/jimmunol.0803590.
334. Correa M, Viaggi C, Escrig MA, et al. Ethanol intake and ethanol-induced locomotion and locomotor sensitization in Cyp2e1 knockout mice. *Pharmacogenet Genomics*. 2009;19(3):217-225. https://doi.org/10.1097/FPC.0b013e328324e726.
335. Roberts AJ, Heyser CJ, Cole M, Griffin P, Koob GF. Excessive ethanol drinking following a history of dependence: Animal model of allostasis. *Neuropsychopharmacology*. 2000;22(6):581-594. https://doi.org/10.1016/S0893-133X(99)00167-0.
336. Vendruscolo LF, Roberts AJ. Operant alcohol self-administration in dependent rats: Focus on the vapor model. *Alcohol*. 2014;48(3):277-286. https://doi.org/10.1016/j.alcohol.2013.08.006.
337. Carlen PL, Corrigall WA. Ethanol tolerance measured electrophysiologically in hippocampal slices and not in neuromuscular junctions from chronically ethanol-fed rats. *Neurosci Lett*. 1980;17(1-2):95-100. https://doi.org/10.1016/0304-3940(80)90068-3.
338. Moghaddam B, Bolinao ML. Biphasic effect of ethanol on extracellular accumulation of glutamate in the hippocampus and the nucleus accumbens. *Neurosci Lett*. 1994;178(1):99-102. https://doi.org/10.1016/0304-3940(94)90299-2.
339. Nixon K, Crews FT. Binge ethanol exposure decreases neurogenesis in adult rat hippocampus. *J Neurochem*. 2002;83(5):1087-1093. https://doi.org/10.1046/j.1471-4159.2002.01214.x.
340. Obernier JA, Bouldin TW, Crews FT. Binge ethanol exposure in adult rats causes necrotic cell death. *Alcohol Clin Exp Res*. 2002;26(4):547-557. https://doi.org/10.1111/j.1530-0277.2002.tb02573.x.
341. Maynard ME, Leasure JL. Exercise enhances hippocampal recovery following binge ethanol exposure. *PLoS One*. 2013;8(9):e76644. https://doi.org/10.1371/journal.pone.0076644.
342. McClain JA, Hayes DM, Morris SA, Nixon K. Adolescent binge alcohol exposure alters hippocampal progenitor cell proliferation in rats: Effects on cell cycle kinetics. *J Comp Neurol*. 2011;519(13):2697-2710. https://doi.org/10.1002/cne.22647.
343. Eckardt MJ, Campbell GA, Marietta CA, Majchrowicz E, Weight FF. Acute ethanol administration selectively alters localized cerebral glucose metabolism. *Brain Res*. 1988;444(1):53-58. https://doi.org/10.1016/0006-8993(88)90912-2.
344. Grünwald F, Schröck H, Biersack HJ, Kuschinsky W. Changes in local cerebral glucose utilization in the awake rat during acute and chronic administration of ethanol. *J Nucl Med*. 1993;34(5):793-798.
345. Campbell GA, Eckardt MJ, Majchrowicz E, Marietta CA, Weight FF. Ethanol-withdrawal syndrome associated with both general and localized increases in glucose uptake in rat brain. *Brain Res*. 1982;237(2):517-522. https://doi.org/10.1016/0006-8993(82)90465-6.
346. Marietta CA, Eckardt MJ, Campbell GA, Majchrowicz E, Weight FF. Glucose uptake in brain during withdrawal from ethanol, phenobarbital, and diazepam. *Alcohol Clin Exp Res*. 1986;10(3):233-236. https://doi.org/10.1111/j.1530-0277.1986.tb05081.x.
347. Zahr NM, Mayer D, Rohlfing T, et al. Brain injury and recovery following binge ethanol: Evidence from in vivo magnetic resonance spectroscopy. *Biol Psychiatry*. 2010;67(9):846-854. https://doi.org/10.1016/j.biopsych.2009.10.028.
348. Zahr NM, Mayer D, Rohlfing T, et al. A mechanism of rapidly reversible cerebral ventricular enlargement independent of tissue atrophy. *Neuropsychopharmacology*. 2013;38(6):1121-1129. https://doi.org/10.1038/npp.2013.11.
349. Zahr NM, Rohlfing T, Mayer D, Luong R, Sullivan EV, Pfefferbaum A. Transient CNS responses to repeated binge ethanol treatment. *Addict Biol*. 2016;21(6):1199-1216. https://doi.org/10.1111/adb.12290.
350. Zhao Q, Fritz M, Pfefferbaum A, Sullivan EV, Pohl KM, Zahr NM. Jacobian maps reveal under-reported brain regions sensitive to extreme binge ethanol intoxication in the rat. *Front Neuroanat*. 2018;12:108. https://doi.org/10.3389/fnana.2018.00108.
351. Zhao Q, Pohl KM, Sullivan EV, Pfefferbaum A, Zahr NM. Jacobian mapping reveals converging brain substrates of disruption and repair in response to ethanol exposure and abstinence in 2 strains of rats. *Alcohol Clin Exp Res*. 2021;45(1):92-104. https://doi.org/10.1111/acer.14496.
352. Bordia T, Zahr NM. The inferior colliculus in alcoholism and beyond. *Front Syst Neurosci*. 2020;14:606345. https://doi.org/10.3389/fnsys.2020.606345.
353. Novier A, Van Skike CE, Diaz-Granados JL, Mittleman G, Matthews DB. Acute alcohol produces ataxia and cognitive impairments in aged animals: A comparison between young adult and aged rats. *Alcohol Clin Exp Res*. 2013;37(8):1317-1324. https://doi.org/10.1111/acer.12110.
354. Faingold CL. The Majchrowicz binge alcohol protocol: An intubation technique to study alcohol dependence in rats. *Curr Protoc Neurosci*. 2008;Chapter 9:Unit 9.28. https://doi.org/10.1002/0471142301.ns0928s44.
355. Baydas G, Tuzcu M. Protective effects of melatonin against ethanol-induced reactive gliosis in hippocampus and cortex of young and aged rats. *Exp Neurol*. 2005;194(1):175-181. https://doi.org/10.1016/j.expneurol.2005.02.003.
356. Grifasi IR, Evans WA, Rexha AD, Sako LW, Marshall SA. A comparison of hippocampal microglial responses in aged and young rodents following dependent and non-dependent binge drinking. *Int Rev Neurobiol*. 2019;148:305-343. https://doi.org/10.1016/bs.irn.2019.10.018.
357. Marsland P, Vore AS, DaPrano E, et al. Sex-specific effects of ethanol consumption in older Fischer 344 rats on microglial dynamics and $A\beta_{(1-42)}$ accumulation. *Alcohol*. 2023;107:108-118. https://doi.org/10.1016/j.alcohol.2022.08.013.

358. Citron M, Oltersdorf T, Haass C, et al. Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature*. 1992;360(6405):672-674. https://doi.org/10.1038/360672a0.
359. Games D, Adams D, Alessandrini R, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature*. 1995;373(6514):523-527. https://doi.org/10.1038/373523a0.
360. Sturchler-Pierrat C, Abramowski D, Duke M, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proc Natl Acad Sci U S A*. 1997;94(24):13287-13292. https://doi.org/10.1073/pnas.94.24.13287.
361. Chishti MA, Yang DS, Janus C, et al. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. *J Biol Chem*. 2001;276(24):21562-21570. https://doi.org/10.1074/jbc.M100710200.
362. De Strooper B, Saftig P, Craessaerts K, et al. Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature*. 1998;391(6665):387-390. https://doi.org/10.1038/34910.
363. De Strooper B, Simons M, Multhaup G, Van Leuven F, Beyreuther K, Dotti CG. Production of intracellular amyloid-containing fragments in hippocampal neurons expressing human amyloid precursor protein and protection against amyloidogenesis by subtle amino acid substitutions in the rodent sequence. *EMBO J*. 1995;14(20):4932-4938. https://doi.org/10.1002/j.1460-2075.1995.tb00176.x.
364. Holcomb L, Gordon MN, McGowan E, et al. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nat Med*. 1998;4(1):97-100. https://doi.org/10.1038/nm0198-097.
365. Borchelt DR, Thinakaran G, Eckman CB, et al. Familial Alzheimer's disease-linked presenilin 1 variants elevate Aβ1-42/1-40 ratio in vitro and in vivo. *Neuron*. 1996;17(5):1005-1013. https://doi.org/10.1016/s0896-6273(00)80230-5.
366. Casas C, Sergeant N, Itier JM, et al. Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated $A\beta_{42}$ accumulation in a novel Alzheimer transgenic model. *Am J Pathol*. 2004;165(4):1289-1300. https://doi.org/10.1016/s0002-9440(10)63388-3.
367. Schmitz C, Rutten BP, Pielen A, et al. Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. *Am J Pathol*. 2004;164(4):1495-1502. https://doi.org/10.1016/s0002-9440(10)63235-x.
368. Oakley H, Cole SL, Logan S, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: Potential factors in amyloid plaque formation. *J Neurosci*. 2006;26(40):10129-10140. https://doi.org/10.1523/jneurosci.1202-06.2006.
369. Oddo S, Caccamo A, Kitazawa M, Tseng BP, LaFerla FM. Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. *Neurobiol Aging*. 2003;24(8):1063-1070. https://doi.org/10.1016/j.neurobiolaging.2003.08.012.
370. Billings LM, Oddo S, Green KN, McGaugh JL, LaFerla FM. Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron*. 2005;45(5):675-688. https://doi.org/10.1016/j.neuron.2005.01.040.
371. Oddo S, Caccamo A, Shepherd JD, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular Abeta and synaptic dysfunction. *Neuron*. 2003;39(3):409-421. https://doi.org/10.1016/s0896-6273(03)00434-3.
372. Oddo S, Vasilevko V, Caccamo A, Kitazawa M, Cribbs DH, LaFerla FM. Reduction of soluble Abeta and tau, but not soluble Abeta alone, ameliorates cognitive decline in transgenic mice with plaques and tangles. *J Biol Chem*. 2006;281(51):39413-39423. https://doi.org/10.1074/jbc.M608485200.
373. Vitek MP, Araujo JA, Fossel M, et al. Translational animal models for Alzheimer's disease: An Alzheimer's Association Business Consortium Think Tank. *Alzheimers Dement (N Y)*.2021;6(1):e12114. https://doi.org/10.1002/trc2.12114.
374. Akhtar A, Gupta SM, Dwivedi S, Kumar D, Shaikh MF, Negi A. Preclinical models for Alzheimer's disease: Past, present, and future approaches. *ACS Omega*. 2022;7(51):47504-47517. https://doi.org/10.1021/acsomega.2c05609.
375. Jullienne A, Trinh MV, Obenaus A. Neuroimaging of mouse models of Alzheimer's disease. *Biomedicines*. 2022;10(2):305. https://doi.org/10.3390/biomedicines10020305.
376. Mullane K, Williams M. Preclinical models of Alzheimer's disease: Relevance and translational validity. *Curr Protoc Pharmacol*. 2019;84(1):e57. https://doi.org/10.1002/cpph.57.
377. Jiang C, Zhang Y, Tang X, et al. IL-6 and IL-1β upregulation and tau protein phosphorylation in response to chronic alcohol exposure in the mouse hippocampus. *Neuroreport*. 2021;32(10):851-857. https://doi.org/10.1097/wnr.0000000000001661.
378. Gong YS, Guo J, Hu K, et al. Chronic ethanol consumption and thiamine deficiency modulate β-amyloid peptide level and oxidative stress in the brain. *Alcohol Alcohol*. 2017;52(2):159-164. https://doi.org/10.1093/alcalc/agw095.
379. Zhao J, Sun X, Yu Z, et al. Exposure to pyrithiamine increases β-amyloid accumulation, Tau hyperphosphorylation, and glycogen synthase kinase-3 activity in the brain. *Neurotox Res*. 2011;19(4):575-583. https://doi.org/10.1007/s12640-010-9204-0.
380. Kim SR, Jeong HY, Yang S, et al. Effects of chronic alcohol consumption on expression levels of APP and Aβ-producing enzymes. *BMB Rep*. 2011;44(2):135-139. https://doi.org/10.5483/BMBRep.2011.44.2.135.
381. Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*. 2012;60(1):188-197. https://doi.org/10.1161/hypertensionaha.112.195511.
382. Wang X, Yu S, Hu JP, et al. Streptozotocin-induced diabetes increases amyloid plaque deposition in AD transgenic mice through modulating AGEs/RAGE/NF-κB pathway. *Int J Neurosci*. 2014;124(8):601-608. https://doi.org/10.3109/00207454.2013.866110.
383. Dong Y, Wu X, Xu Z, Zhang Y, Xie Z. Anesthetic isoflurane increases phosphorylated tau levels mediated by caspase activation and Aβ generation. *PLoS One*. 2012;7(6):e39386. https://doi.org/10.1371/journal.pone.0039386.
384. Li Y, Ding R, Ren X, et al. Long-term ketamine administration causes Tau protein phosphorylation and Tau protein-dependent AMPA receptor reduction in the hippocampus of mice. *Toxicol Lett*. 2019;315:107-115. https://doi.org/10.1016/j.toxlet.2019.08.023.
385. Huang D, Yu M, Yang S, et al. Ethanol alters APP processing and aggravates Alzheimer-associated phenotypes. *Mol Neurobiol*. 2018;55(6):5006-5018. https://doi.org/10.1007/s12035-017-0703-3.
386. Day SM, Gironda SC, Clarke CW, et al. Ethanol exposure alters Alzheimer's-related pathology, behavior, and metabolism in APP/PS1 mice. *Neurobiol Dis*. 2023;177:105967. https://doi.org/10.1016/j.nbd.2022.105967.
387. Ledesma JC, Rodríguez-Arias M, Gavito AL, et al. Adolescent binge-ethanol accelerates cognitive impairment and β-amyloid production and dysregulates endocannabinoid signaling in the hippocampus of APP/PSE mice. *Addict Biol*. 2021;26(1):e12883. https://doi.org/10.1111/adb.12883.
388. Hoffman JL, Faccidomo S, Kim M, et al. Alcohol drinking exacerbates neural and behavioral pathology in the 3xTg-AD mouse model of Alzheimer's disease. *Int Rev Neurobiol*. 2019;148:169-230. https://doi.org/10.1016/bs.irn.2019.10.017.

389. Sanna PP, Cabrelle C, Kawamura T, et al. A history of repeated alcohol intoxication promotes cognitive impairment and gene expression signatures of disease progression in the 3xTg mouse model of Alzheimer's disease. *eNeuro*. 2023;10(7):ENEURO.0456-22.2023. https://doi.org/10.1523/eneuro.0456-22.2023.
390. Jimenez Chavez CL, Van Doren E, Matalon J, et al. Alcohol-drinking under limited-access procedures during mature adulthood accelerates the onset of cognitive impairment in mice. *Front Behav Neurosci*. 2022;16:732375. https://doi.org/10.3389/fnbeh.2022.732375.
391. Szumlinski KK, Herbert JN, Mejia Espinoza B, Madory LE, Scudder SL. Alcohol-drinking during later life by C57BL/6J mice induces sex- and age-dependent changes in hippocampal and prefrontal cortex expression of glutamate receptors and neuropathology markers. *Addict Neurosci*. 2023;7:100099. https://doi.org/10.1016/j.addicn.2023.100099.
392. Downs AM, Catavero CM, Kasten MR, McElligott ZA. Tauopathy and alcohol consumption interact to alter locus coeruleus excitatory transmission and excitability in male and female mice. *Alcohol*. 2023;107:97-107. https://doi.org/10.1016/j.alcohol.2022.08.008.
393. Tucker AE, Alicea Pauneto CDM, Barnett AM, Coleman LG Jr. Chronic ethanol causes persistent increases in Alzheimer's tau pathology in female 3xTg-AD mice: A potential role for lysosomal impairment. *Front Behav Neurosci*. 2022;16:886634. https://doi.org/10.3389/fnbeh.2022.886634.
394. Barnett A, David E, Rohlman A, et al. Adolescent binge alcohol enhances early Alzheimer's disease pathology in adulthood through proinflammatory neuroimmune activation. *Front Pharmacol*. 2022;13:884170. https://doi.org/10.3389/fphar.2022.884170.
395. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E episilon4 magnifies lifestyle risks for dementia: A population-based study. *J Cell Mol Medicine*. 2008;12(6b):2762-2771. https://doi.org/10.1111/j.1582-4934.2008.00296.x.
396. Chandrashekar DV, Steinberg RA, Han D, Sumbria RK. Alcohol as a modifiable risk factor for Alzheimer's disease—Evidence from experimental studies. *Int J Mol Sci*. 2023;24(11):9492. https://doi.org/10.3390/ijms24119492.
397. Garcia J, Chang R, Steinberg RA, et al. Modulation of hepatic amyloid precursor protein and lipoprotein receptor-related protein 1 by chronic alcohol intake: Potential link between liver steatosis and amyloid-β. *Front Physiol*. 2022;13:930402. https://doi.org/10.3389/fphys.2022.930402.
398. Chiu WC, Tsan YT, Tsai SL, Chang CJ, Wang JD, Chen PC. Hepatitis C viral infection and the risk of dementia. *Eur J Neurol*. 2014;21(8):1068-e59. https://doi.org/10.1111/ene.12317.
399. Tyas SL. Alcohol use and the risk of developing Alzheimer's disease. *Alcohol Res Health*. 2001;25(4):299-306.