THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 8

REVIEW ARTICLE

Linking alcohol use to Alzheimer's disease: Interactions with aging and APOE along immune pathways

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OPEN ACCESS

PUBLISHED
31 August 2024

CITATION
Monnig, M. and Shah K., 2024. Linking alcohol use to Alzheimer's disease: Interactions with aging and APOE along immune pathways. Medical Research Archives, [online] 12(8).
https://doi.org/10.18103/mra.v12i8.5228

DOI
https://doi.org/10.18103/mra.v12i8.5228

ISSN
2375-1924

ABSTRACT

Although it is known that APOE genotype is the strongest genetic risk factor for late-onset Alzheimer's disease, development is a multifactorial process. Alcohol use is a contributor to the epidemic of Alzheimer's disease and related dementias in the US and globally, yet mechanisms are not fully understood. Carriers of the APOE ε4 allele show elevated risk of dementia in relation to several lifestyle factors, including alcohol use. In this review, we describe how alcohol interacts with APOE genotype and aging with potential implications for Alzheimer's disease promotion. Age-related immune senescence and "inflammaging" (i.e., low-grade inflammation associated with aging) are increasingly recognized as contributors to age-related disease. We focus on three immune pathways that are likely contributors to Alzheimer's disease development, centering on alcohol and APOE genotype interactions, specifically: 1) microbial translocation and immune activation, 2) the senescence associated secretory phenotype, and 3) neuroinflammation. First, microbial translocation, the unphysiological movement of gut products into systemic circulation, elicits a proinflammatory response and increases with aging, with proposed links to Alzheimer's disease. Second, the senescence associated secretory phenotype is a set of intercellular signaling factors, e.g., proinflammatory cytokines and chemokines, growth regulators, and proteases, that drives cellular aging when senescent cells remain metabolically active. The senescence associated secretory phenotype can drive development of aging-diseases such as Alzheimer's disease. Third, neuroinflammation occurs via numerous mechanisms such as microglial activation and is gaining recognition as an etiological factor in the development of Alzheimer's disease. This review focuses on interactions of alcohol with APOE genotype and aging along these three pathways that may promote Alzheimer's disease. Further research on these processes may inform development of strategies to prevent onset and progression of Alzheimer's disease and to delay associated cognitive decline.

Keywords: alcohol, heavy drinking, moderate drinking, Alzheimer's disease, APOE genotype, immune system, neuroinflammation, microbial translocation, senescence associated secretory phenotype

I. Introduction

Alcohol use is a likely contributor to the epidemic of Alzheimer's disease (AD) and related dementias in the US and globally. In the US, 6.7 million people are living with AD, including 1 in 9 adults over age 65[1]. Dominantly inherited (or "early onset") AD is caused by rare mutations and represents <1% of AD cases. The late-onset form of AD represents the vast majority of cases. The APOE gene is the strongest risk factor for late-onset AD[2,3]. Humans possess two copies of APOE. Allelic variants ε2, ε3, and ε4 occur at frequencies of ~8%, 78%, and 14%, respectively[4]. Having one or two ε4 alleles increases AD risk by 3 or 15 times, respectively[4,5]. The ε4 allele occurs at a disproportionately high frequency in AD cases (~40%)[4]. The APOE ε4 allele also is associated with cognitive decline in non-demented individuals during mid-to-late life[6]. In practice, population-based research often compares ε 4 carriers (ε3/ ε4, ε4/ ε4) versus non-carriers due to low rates of ε4 homozygotes (~1-4%).

Despite vast research strides, the cause of late-onset AD remains unknown. The amyloid cascade model posited that deposition of amyloid-β in the brain causes development of AD[7]. Recently, this model has been expanded to incorporate microbial seeding of the brain and chronic neuroinflammation as possible causal factors[8-10]. Innate immune mechanisms along the gut-brain axis are emerging as key players in this process. In particular, there are several immune pathways that are affected by age and APOE and have known neurobiological significance.

This focused review examines potential contributions of alcohol to the development of late-onset AD, with an emphasis on interactions of alcohol with aging and APOE genotype. We begin by establishing a historical context for the relationship between alcohol and AD. Next, we discuss relevant models of alcohol's interaction with age and APOE genotype on three key immune pathways that are likely contributors to AD development, specifically: 1) microbial translocation and immune activation, 2) the senescence associated secretory phenotype (SASP), and 3) neuroinflammation.

I. BACKGROUND AND CONTEXT ON ALCOHOL USE IN RELATION TO ALZHEIMER'S DISEASE

In the United States, 55.3% of adults report any alcohol use and 26.5% report binge drinking in the past month[11]. Moreover, 72% of adults ages 45-64 and 55% of adults ages 65+ used alcohol in the past year[12]. Further, 11% of adults ages 45-64 and 4% of adults ages 65+ engage in high-risk drinking (5+ for men, 4+ for women on a given day) at least weekly[12]. High-risk drinking has increased 49% for 45-64 year olds and 65% in 65+ individuals in less than two decades[12]. Chronic heavy drinking puts older adults at heightened risk for cognitive decline, dementia, serious infections, frailty, falls, hospitalization, and overall mortality[13-21]. The number of older adults in the US is expected to nearly double by 2060[22], yet understanding of alcohol use and its effects during the age process remains limited.

The association of alcohol use disorder with dementia is substantial. A study conducted nationwide in France found that alcohol use disorder is associated with >3-fold increase in dementia risk, stronger than the association of smoking, obesity, hypertension, low education, or depression[23]. Similarly, after adjusting for common risk factors, an Australian population-based, case-control study linked mid-life alcohol use disorder to development of dementia[24]. Like the ε4 allele, heavy drinking is associated with faster AD onset[25]. In fact, the reduction in time to AD onset for heavy drinking, at 4 years, surpasses that of ε4 carriage, at 2.7 years.[25] Individuals with alcohol use disorder exhibit accelerated brain aging, with brain age averaging 4 years older than chronological age[26].

The effects of long-term, but non-disordered, alcohol use are less unclear. This pattern is representative of most US adults who consume alcohol. Moderate drinking was long thought to protect against age-related brain atrophy, cognitive decline, and dementia. However, these purported protective effects have come into

question. A recent meta-analysis found that the maximum protective effect of alcohol against dementia is achieved at a modest dose of 6 g/day, equivalent to half of one standard drink[27]. Notably, many older studies defined "moderate" drinking as 2-4 drinks per day[28]. There is growing awareness of sampling biases in observational studies. A systematic review found an association of light to moderate alcohol use with lower risk of cognitive decline or dementia[29]. Yet the review noted many limitations of observational studies, including non-standardization of alcohol use, lack of control for confounds, misclassification of former drinkers, exclusion of heavy drinkers, and survivor bias[29].

Recent longitudinal studies suggest that moderate drinking alcohol is harmful or at least not protective for brain health and cognition in aging[14,30-33]. For example, accounting for abstainer bias, wherein those who abstain have a greater burden of health conditions independent of alcohol use, eliminated the "J-shaped curve" and instead gave evidence of a negative association between midlife alcohol use and cognitive performance 25 years later[33]. A 30-year prospective cohort study found no protective effect of light or moderate drinking over abstinence[32]. Instead, higher alcohol consumption correlated with lower gray matter density, hippocampal atrophy, and white matter degradation[32]. Similarly, an MRI analysis of over 36,000 individuals in the UK Biobank detected a negative association of alcohol use with gray and white matter volumes and white matter microstructural indices at just 1-2 drinks per day[34].

In summary, several decades of research studies have asked, "Is moderate drinking protective against dementia?" The highly discrepant set of answers to this question points to the importance of methodological rigor and also suggests that individual risk factors are at play. Perhaps a more salient question is, "For which individuals does alcohol use pose a potential risk factor for dementia?"

This review examines aging and APOE genotype as likely moderators of the effect of alcohol on immunological and neurobiological mechanisms linked to AD (Figure 1). Prior research gives reason to posit interactions of alcohol with APOE on pathways leading to development of AD. First, APOE is known to moderate the association of alcohol use with key health outcomes related to AD, including coronary heart disease[35] and cerebrovascular disease[36]. Second, ε4 carriers have a higher risk of dementia in relation to several lifestyle factors, not limited to alcohol use but also including physical inactivity, diet, and smoking[37]. Third, APOE ε4 moderates the association of alcohol with cognitive and neurobiological outcomes. Prospective population-based studies report that moderate or heavy alcohol use increases risk of dementia in ε4 carriers but not non-carriers[37-40]. For ε4 carriers (but not non-carriers), drinking at least once per month at midlife was associated with an odds ratio of 7.4 for dementia, relative to never drinking[37]. Similarly, ε4 carriers, but not non-carriers, who consumed moderate alcohol in late life showed cognitive decline[41]. At the same time, other studies have yielded contrary or null findings for alcohol-APOE interactions on cognition[42,43].

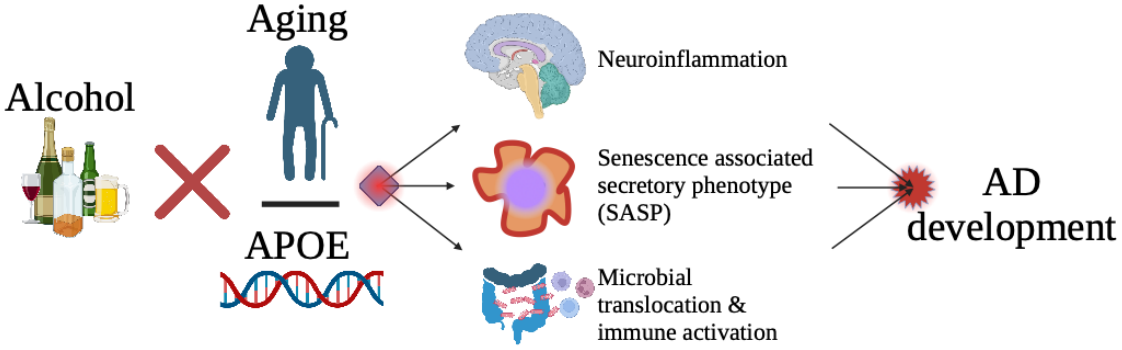

Figure 1. Schematic diagram of the model wherein alcohol interacts with aging and/or APOE genotype to promote AD development through specific pathways of neuroinflammation, the SASP, and microbial translocation and related immune activation. Created by the author using Biorender.

Moreover, there is evidence for an alcohol-aging interaction on AD development. Age-related immune senescence and "inflammaging" (chronic low-grade inflammation associated with aging) are increasingly recognized as contributors to age-related diseases[44,45]. Alcohol use disorder is a recognized risk factor for AD and related dementias[23,29,46]. Even with moderate drinking, it is widely observed that alcohol affects older individuals differently from younger individuals. For example, acute moderate alcohol causes greater disruptions to cognition and neural activity in older adults[47-50]. Older age may present a sensitive period during which alcohol exerts more deleterious effects on key pathways, ultimately promoting AD neuropathology.

II. CANDIDATE MECHANISMS OF ALCOHOL USE AS A CONTRIBUTOR TO ALZHEIMER'S DISEASE

II.A. MICROBIAL TRANSLOCATION AND IMMUNE ACTIVATION

Alcohol impacts microbial translocation and innate immune function: Alcohol consumption can induce systemic inflammation through its effects on the GI tract and on circulating immune cells. Alcohol use perturbs composition of the intestinal microbiota and induces intestinal hyperpermeability via disruption of tight junction proteins[51-54]. In turn, these effects lead to microbial translocation, i.e., the unphysiological movement of microbes from the gut into systemic circulation[51,52]. The concentration of lipopolysaccharide (LPS) in plasma is used widely as a marker of microbial translocation (see Table 1). Also known as endotoxin, LPS is a component of cell walls of Gram-negative bacteria and a ligand for the innate immune receptor, toll-like receptor 4 (TLR4)[55]. Binding of LPS to TLR4 on monocytes or macrophages initiates a proinflammatory immune cascade. Two accessory proteins necessary for binding of LPS to TLR4 are LPS binding protein (LBP) and soluble cluster of differentiation 14 (sCD14)[56,57]. Both LBP and sCD14 are upregulated as part of the acute phase response. Recognition of LPS by TLR4 stimulates monocytes and macrophages to secrete pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6)[58,59].

Consistent with the premise that heavy drinking causes microbial translocation, individuals with alcohol use disorder or heavy drinking exhibit chronic elevations in LPS, LBP, sCD14, and pro-inflammatory cytokines[60-69]. These elevations tend to remediate within weeks of alcohol cessation[63,67,68]. Whereas alcohol's gastrointestinal effects are most marked with chronic heavy use, experimental studies in humans have shown that a single binge-level dose can cause intestinal damage and/or microbial translocation in healthy humans[70,71]. For example, a dose that raised blood alcohol level (BAL) to approximately .09 g/dL caused increases in LPS, LBP, and sCD14 at 30 minutes through 24 hours[70]. Thus, alcohol activates a pro-inflammatory cascade through pathways mediated by the gut and innate immune cells.

Table 1: Biomarkers of microbial translocation and immune function

	Immune pathway/process	Effect of chronic heavy alcohol
Lipopolysaccharide (LPS)	Microbial translocation	↑
LPS binding protein (LBP)	Immune response to LPS	↑
Soluble CD14 (sCD14)	Monocyte activation	↑
Cytokines/chemokines (TNF-α, MCP-1, IL-6)	Pro-inflammatory signaling	↑

Effects of alcohol on these pathways are dose-dependent: Alcohol at moderate doses may actually reduce pro-inflammatory cytokine production, according to *in vitro* human cell studies

and rodent models[72]. Moderate alcohol in healthy organisms may stimulate immune response, thereby increasing microbial clearance[73]. Although dose comparison studies in humans are lacking, a simian model of moderate vs. heavy drinking found that moderate doses upregulated transcription and activation of metabolic and immune signaling genes, including APOE[74]. In contrast, heavy alcohol elicited a resting pro-inflammatory state paired with suppressed response to an acute immune insult (i.e., LPS stimulation)[74].

APOE genotype moderates innate immune response: Rates of AD are elevated 3 times in heterozygous ε 4 carriers and 15 times in homozygous ε 4 carriers[2-5]. However, the ubiquity of apolipoprotein E (apoE), encoded by the APOE gene, throughout the body has made it difficult to pinpoint mechanisms by which it leads to AD development. One possibility is through interactions with the immune system. Apolipoproteins support innate immune response to microbial pathogens such as LPS. Immune response to insults such as systemic LPS may be dysregulated in APOE ε 4 carriers in ways that ultimately promote AD neuropathology. Apolipoprotein dynamics appear to play a determining role in the differential innate immune responses observed between ε 4 carriers and non-carriers, in that different APOE genotypes exhibit differential capacity for apoE production and LPS neutralization[75-80]. In clinical research, chronic low-grade inflammation increased risk and hastened onset of AD in ε 4 carriers, but not non-carriers[81]. It is speculative that response to alcohol is shifted toward pro-inflammatory signaling in ε 4 carriers, thereby blocking the anti-inflammatory effects of moderate alcohol and increasing risk for AD. Consistent with this premise, alcohol use was positively associated with inflammatory cytokine IL-6 in APOE ε 4 carriers, but not in non-carriers[82].

Aging is associated with microbial translocation: In animal models, aging causes alterations in the gut microbiota and intestinal barrier permeability that lead to higher plasma LPS, LBP, and sCD14 levels, indicative of microbial translocation[83-86]. In older but not younger rats, LPS exposure led to liver inflammation, pointing to age-related vulnerability to sequela of microbial translocation[87]. In human observational studies, LBP is higher with age, particularly in those with metabolic syndrome and poorer physical functioning[88-90]. Similarly, sCD14 predicts cardiovascular disease risk and all-cause mortality in older adults[91]. Age-related microbial translocation is a probable source of the chronic low-level inflammation observed in aging[92].

Biomarkers of microbial translocation and immune function are linked to Alzheimer's disease development: Biomarkers in Table 1 are relevant to development of AD. Plasma LPS is elevated in individuals with AD compared to controls[93]. A study comparing gut microbiota composition in individuals with AD and controls found significant microbiota alterations in AD that were associated with cerebrospinal fluid (CSF) markers of amyloid and tau burden[94]. Higher gut levels of pathogenic Gram-negative bacteria may contribute to elevated plasma LPS in AD[94]. Whereas it was previously believed that LPS does not cross from periphery into brain under physiological conditions, a novel immunoassay study in rodents recently showed that LPS does enter the brain via lipoprotein transport mechanisms[95]. Further, recent human studies have identified elevated LPS levels in postmortem brain tissue, including cortex and hippocampus, of individuals with AD[8,96]. These findings suggest that systemic LPS has significance for the development of AD.

Both LBP and sCD14 are significant due to their role as acute phase proteins that reflect immune response to LPS and are emerging as predictors of AD development. In community-dwelling adults over a 12-year period, LBP at baseline predicted AD development, with a one-unit standard deviation elevation in LBP associated with 33% higher odds of AD[97]. In the Framingham Heart Study cohort, a one-unit standard deviation elevation in sCD14 was linked to a 12% higher risk of incident dementia over a 10-year period[98].

Similarly, cytokines TNF-α and IL-6 and chemokine MCP-1 are important markers of chronic inflammation in the context of AD development. Studies comparing these cytokines in AD and healthy individuals report variable results. A meta-analysis concluded that TNF-α and IL-6 did not differ significantly in cross-sectional comparisons of AD and healthy controls[99]. However, other studies suggest a prospective association of these cytokines with development of dementia. A meta-analysis of prospective studies found that elevated IL-6 was associated with 1.42 times the odds of cognitive decline[100]. In a community-based study, individuals who developed incident dementia during a 2-year follow-up had significantly higher TNF-α[101]. Chemokine MCP-1 is elevated in AD and correlates with severity of cognitive impairment[102,103]. It also predicted cognitive decline over a 2-year period in individuals with AD[102].

II.B. THE SENESCENCE ASSOCIATED SECRETORY PHENOTYPE

The senescence associated secretory phenotype (SASP) is an index of cellular aging: Cellular aging manifests in secretion of a set of intercellular signaling factors, e.g., proinflammatory cytokines and chemokines, growth regulators, and proteases, known as the SASP[104,105]. Cellular senescence is induced by a wide range of intracellular and extracellular stressors known to arrest cell growth and proliferation, which serves to target potential malignancies[105]. The SASP develops when senescent cells remain metabolically active, secreting a wide range of interleukins, chemokines, growth factors, proteases, and extracellular matrix components[105]. Although the SASP likely evolved as a tumor suppressive mechanism, the accumulation of cells with this phenotype over time and with age can itself drive disease[105-107]. The SASP is one of many candidate indices of biological aging[108]. One caveat is that SASP biomarkers, including cytokines and chemokines discussed here, are not specific to aging[108].

Cellular senescence drives aging at the organismal level: The mechanisms that translate cellular senescence into decline of physical condition are an area of active scientific investigation. One such mechanism is "inflammaging," or chronic, low-level, sterile inflammation[44,45]. Possible causes of inflammaging include accumulated cellular damage, microbial translocation, senescence of the immune system, and the SASP itself[44,45,106]. The accumulation of metabolically active senescent cells expressing the SASP has pro-inflammatory effects on surrounding cells and tissue. Core elements of the SASP, including IL-6, IL-8, MCP-1, and TNF-α, are strongly linked to other indices of biological aging across clinical studies[109-117]. To the extent that lifestyle factors such as poor diet and inactivity promote chronic inflammation, inflammaging may best be considered both a cause and a consequence of age-related physical decline[45]. Clinical research directly linking APOE genotype to the SASP is limited at present. However, preclinical evidence indicates that ApoE4 promotes development of senescence in neurons[118].

Alcohol may exacerbate SASP mechanisms: Alcohol is a potential driver of inflammaging in older individuals and APOE ε 4 carriers. Previous studies have investigated acute or chronic effects of alcohol on cytokines and chemokines that are markers of the SASP. Cytokines IL-6 and TNF-α and chemokines IL-8 and MCP-1 are core components of the SASP[105-107,119,120] that also show effects of acute alcohol exposure in numerous research studies[67,121-124]. Alcohol-induced changes in these markers may be due to alcohol's activation of transcription factors, particularly nuclear factor kappa light chain enhancer of B cells (NF-κB) and release of nuclear proteins such as high-mobility group box 1 (HMGB1)[125-130]. Signaling via NF-κB and HMGB1 pathways drives SASP expression[131,132]. Alcohol affects levels of many cytokines and chemokines, not all of which are SASP components. However, studies showing reduced telomere length, accelerated DNA methylation aging, and induction of SASP in relation to heavy alcohol use support the premise that alcohol may promote cellular aging and senescence[133-139].

II.C. NEUROINFLAMMATION

Neuroinflammation contributes to Alzheimer's disease development: The traditional amyloid cascade hypothesis has evolved to incorporate microbial seeding of the brain and chronic neuroinflammation as etiological factors in development of AD[8-10]. In the brain, ApoE is synthesized as a primary apolipoprotein[140]. As noted above, ApoE participates in removing amyloid-β from brain, and the ApoE4 isoform is less competent at amyloid-β clearance[140]. In addition, ε 4 carriage is associated with greater pro-inflammatory response in the brain's glial cells and reduced capacity for neuroprotective functions[141,142]. Mechanisms by which ApoE4 contributes to neuroinflammation in AD are reviewed in detail elsewhere[143].

Until recently, it was believed that the brain was a sterile environment not directly vulnerable to microbial stimuli such as LPS. However, a recent study showed that LPS is present in rat brain under physiological conditions[95], suggesting that there is movement of microbial products from the periphery into the CNS in the absence of disease. Even without penetrating the blood-brain barrier, systemic LPS induces pro-inflammatory CNS response[124]. Consequently, LPS-induced inflammation, both systemic and in the CNS, is gaining attention as a possible contributor to AD development[144]. In addition to stimulating pro-inflammatory response in glial cells, LPS prevents clearance of amyloid-β from the brain[145]. In AD, LPS colocalizes with amyloid plaques, and LPS levels are greatly elevated in the cortex and hippocampus of postmortem AD brains, relative to healthy aged adults[8,9,96]. In sum, neuroinflammation related to pathogenic stimuli such as LPS is central to evolving understanding of AD.

Magnetic resonance spectroscopy (MRS) detects neurometabolic perturbations related to AD development: Neural correlates of neuroinflammation can be measured noninvasively using MRS. At present, there is no direct method to safely and non-invasively measure neuroinflammation in living humans. However, MRS is a powerful, widely available, and reproducible imaging method that detects subtle differences in concentrations of brain metabolites. Elevated **choline** and **myo-inositol** and lower **N-acetyl-aspartate** (**NAA**) levels are consistently found in neuroinflammatory diseases[146]. Choline is a marker of cellular membrane turnover[147]. Myo-inositol, sometimes referred to as a glial marker, is more accurately described as a part of second messenger systems and an osmotic regulator[147]. Choline and myo-inositol often are elevated in neuroinflammatory and neurodegenerative conditions. A marker of neuronal density and viability, NAA typically is decreased in disease. Derangement of any of these metabolite systems has implications for brain health in aging.

Age-related neuroinflammation has its roots in microglial activation, and it primes the brain to produce a stronger response to internal and external stressors and inflammatory stimuli[148-151]. Human MRS studies link age-related neurometabolic changes with deteriorations in cognition and physical health[152-156]. Older age is linked to higher levels of myo-inositol and choline in various brain regions[157-164]. This pattern has been interpreted as glial proliferation, glial activation, and/or increased cellular turnover[157-162,164]. Similarly, studies consistently link older age with lower N-acetyl-aspartate (NAA), which is interpreted as indicating decreased neuronal volume and/or density[159,163,164]. The NAA/myo-inositol ratio also is relevant to age-related neuropathology and cognitive decline[152,153,165].

Neurometabolic alterations are implicated in AD and predict its development: Elevated choline and myo-inositol and reduced NAA consistently are implicated in AD. A recent meta-analysis of MRS studies comparing AD to control groups concluded that AD groups exhibited significantly lower NAA/Cr and higher choline/Cr, myo-inositol/Cr, and myo-inositol/NAA ratios in posterior cingulate and parietal cortex[166]. [Metabolites often are reported as ratios to creatine (Cr),

although the field is moving away from this convention due to the potential for confounding when Cr is not stable[167]]. Meta-analytic effects sizes were medium to large[166]. In addition, MRS has been used in cognitively healthy samples to detect neurometabolic perturbations associated with ε 4genotype and preclinical AD pathology. One MRS study compared cognitively normal individuals with and without abnormal CSF levels of Aβ42, an established marker of AD pathology[156]. Those with abnormal Aβ42 had higher myo-inositol/Cr in precuneus and posterior cingulate cortex[156]. Among cognitively normal Aβ42-*negative* individuals, APOE ε 4 carriers had higher myo-inositol/Cr than non-carriers[156]. In a study of cognitively healthy older individuals, higher myo-inositol/Cr and choline/Cr were associated with amyloid-β deposition on positron emission tomography (PET).[154]

A prospective longitudinal study with 7-year follow-up quantified NAA/Cr, myo-inositol/Cr, and NAA/myo-inositol in 289 cognitively normal individuals with mean age 75[152]. Those who went on to develop AD seven years later already had lower NAA/Cr, higher myo-inositol/Cr, and lower NAA/myo-inositol at baseline, compared to those who remained cognitively normal[152]. Baseline NAA/myo-inositol differentiated participants who did versus did not develop AD with high specificity and sensitivity[152]. Also, ε 4 homozygotes had higher myo-inositol/Cr and lower NAA/myo-inositol compared to non-carriers[152]. Another longitudinal study followed cognitively healthy older adults for an average of 2.8 years, reporting that lower NAA/myo-inositol at baseline predicted transition to mild cognitive impairment at follow-up[153]. In the same cohort, lower NAA/myo-inositol and higher myo-inositol/Cr at baseline predicted greater accumulation of amyloid-β on PET[165]. Together, the findings point to alterations in myo-inositol, choline, and NAA/myo-inositol as a risk factor for AD development.

Alcohol, acute or chronic, affects neurometabolic pathways implicated in AD: Alcohol affects multiple neurotransmitter systems and neurometabolites. As with the immune system, alcohol's effects on neurometabolism greatly depend on dose, timecourse, and chronicity of alcohol consumption. In MRS studies of chronic heavy drinkers, the most consistent finding is lower NAA during early abstinence from alcohol[168]. In observational studies of moderate to heavy drinkers who are abstinent at the time of imaging, quantity of recent alcohol consumption correlates with higher choline levels, suggesting a neuroinflammatory response[169-171]. A recent meta-analysis of observational MRS studies reported lower NAA, choline, and GABA in chronic heavy drinkers relative to controls[172]. Meta-analytic findings were nonsignificant for myo-inositol[172]. In regard to acute alcohol effects, a handful of MRS studies have found significant changes in changes in NAA, choline, and myo-inositol concentrations during ascending, peak, and descending blood alcohol (~.05-.07)[173-175]. Findings were mixed, likely due to differences in route of administration (oral vs. intravenous), brain regions of interest, and time course of MRS measurements[173-175].

APOE genotype is related to markers of brain health in cognitively normal individuals: In terms of brain structural differences, APOE ε 4 carriers show smaller volumes in medial temporal lobe in young adult samples, with minimal effects in other regions[176]. In healthy adults (mean age 39) with normal cognition, there was no main effect of APOE genotype on MRI volumes of precuneus or hippocampus, amyloid deposition, brain glucose metabolism, or CSF markers[177]. However, there was an age by APOE interaction for amyloid deposition, with ε 4 carriers over age 50 showing greater deposition[177]. Another study found no effect of APOE genotype on gray matter volume or cerebral glucose metabolism but did identify greater amyloid deposition in cognitively healthy APOE carriers with mean age 49[178]. Furthermore, there is evidence from postmortem analysis that APOE ε 4 interacts with molecular brain aging to synergistically increase risk for AD[179]. Few studies have addressed the interaction of age and APOE genotype on cerebral metabolites. One MRS study

found an interaction of age with APOE ε 4 on choline and myo-inositol in cognitively intact individuals ages 50-86[180]. However, a similar study found no interaction of age and APOE on MRS metabolites in cognitively healthy individuals ages 20-40 years versus 60-85 years[161].

III. Conclusion

Alcohol is known to have pro-inflammatory effects on both peripheral and central immune systems via innate immune mechanisms[181-183]. Whether alcohol promotes or dampens inflammation depends largely on dose and chronicity of exposure. Acute low to moderate alcohol doses tend to have anti-inflammatory effects in concert with immune mobilization, whereas chronic and/or high doses tend to exert pro-inflammatory effects in concert with immune suppression[72,183-187]. However, contextual and individual factors such as age, APOE genotype, and chronic health conditions have not been investigated in controlled human research as potential moderators of alcohol's immune effects. Age is a key factor, as immune senescence and "inflammaging" (i.e., chronic low-grade inflammation associated with aging) are increasingly recognized as contributors to age-related diseases[44,45]. Overwhelming evidence links circulating inflammatory biomarkers to cognitive impairment, brain aging, morbidity, and mortality in older adults[188-196]. This review examined the potential for alcohol to exacerbate inflammation related to aging and/or APOE genotype via several pathways, specifically 1) microbial translocation and immune activation, 2) the SASP, and 3) neuroinflammation. Overall, there is evidence that alcohol may interact with age and/or APOE genotype along these pathways to promote processes that increase risk for AD development.

Conflict of Interest:

None.

Funding:

This research was supported by the National Institute on Alcohol Abuse and Alcoholism grant K23AA024704 (PI: M. Monnig) and the National Institute on General Medical Sciences grant P20GM130414 (PI: P. Monti).

Acknowledgements:

None.

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