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Aging, sex, metabolic and life experience factors: Contributions to neuro-inflammaging in Alzheimer's disease research

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ABSTRACT

Alzheimer's disease (AD) is prevalent around the world, yet our understanding of the disease is still very limited. Recent work suggests that the cornerstone of AD may include the inflammation that accompanies it. Failure of a normal pro-inflammatory immune response to resolve may lead to persistent central inflammation that contributes to unsuccessful clearance of amyloid-beta plaques as they form, neuronal death, and ultimately cognitive decline. Individual metabolic, and dietary (lipid) profiles can differentially regulate this inflammatory process with aging, obesity, poor diet, early life stress and other inflammatory factors contributing to a greater risk of developing AD. Here, we integrate evidence for the interface between these factors, and how they contribute to a pro-inflammatory brain milieu. In particular, we discuss the importance of appropriate polyunsaturated fatty acids (PUFA) in the diet for the metabolism of specialised pro-resolving mediators (SPMs); raising the possibility for dietary strategies to improve AD outlook.

1. Introduction

Worldwide, more than 50 million people have dementia, with nearly 10 million new cases every year (Collaborators, 2022). Alzheimer's disease (AD) is the most common form of dementia and it has substantial physical, psychological, social and economic impacts (Weller and Budson, 2018; Silva et al., 2019). Around 95% of AD cases are late-onset, with disease manifesting at around 65 years of age (Bali et al., 2012). Late-onset AD is considered to be sporadic, while early-onset AD is associated with autosomal dominant mutations in specific genes and appears much earlier, with symptoms developing around 45–64 years (Reitz et al., 2020). Despite significant research advances, we still have no cure for dementia or AD, and we still have no real understanding of the causes, particularly for late-onset AD, or the mechanisms underlying

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disease onset and progression. Even though overall promising results from clinical studies using anti-amyloid-beta (Aβ) antibodies such as aducanumab, lecanemab or donanemab are emerging and further support the role of Aβ aggregates in AD pathology, the pronounced resolution of amyloid plaques by these therapeutic antibodies does not correlate well with the major cognitive endpoints (Budd Haeberlein et al., 2022; van Dyck et al., 2023; Mintun et al., 2021; Sims et al., 2023). In fact, while reducing up to 60% or even 80% of the amyloid burden detected by PET imaging, e.g. with the FDA-approved lecanemab and with donanemab, respectively, the progression of cognitive decline in AD patients is only mildly attenuated but not at all halted or reversed (Mintun et al., 2021; Filippi et al., 2022). Such moderate therapeutic effects of these Aβ antibodies on cognitive decline are at the cost of considerable unwanted side effects such as amyloid-related imaging abnormalities (ARIA) caused by vasogenic oedema (ARIA-E) and hemosiderin deposits involving microhemorrhages (ARIA-H). Recent studies with donanemab also suggest this therapeutic leads to accelerated decreases in brain volume (Mintun et al., 2021; Filippi et al., 2022). Thus, therapeutic targeting of Aβ has finally reached the clinic, however, with moderate effects, and further therapeutic strategies and deeper understanding are warranted for more efficient interference with the underlying pathology.

Recent research suggests that chronic activation of the brain's innate immune cells, microglia, leads to central inflammation that is an important contributor to neurodegeneration, cognitive decline, and AD pathogenesis (Hoeijmakers et al., 2016; De Luca et al., 2016) and therefore a potential target for treatment. Under normal conditions, inflammation helps clear pathogens and return tissue to homeostasis before being downregulated by cells entering a state of resolution. If resolution fails, inflammatory mediators drive chronic neuroinflammation and contribute to AD pathogenesis. The resolution phase is dysregulated in AD (Hopperton et al., 2018) and hypothetically disrupts mechanisms such as those involving specialized pro-resolving mediators (SPMs), which can increase amyloid phagocytosis and reduce amyloid toxicity *in vitro (*Zhu et al., 2016*)*. Evidence suggests that dietary n-3 polyunsaturated fatty acids (PUFAs) are crucial to SPM production in the brain, (Rey et al., 2019) including in microglia (Madore et al., 2020). Notably, SPM levels are decreased in post-mortem brains of subjects with AD, (Wang et al., 2015) likely contributing to the failure to resolve inflammation (Laye et al., 2018; Lee et al., 2020). For example, the SPM lipoxin A4 (LXA4) was not only confirmed to be reduced in post-mortem hippocampal tissue but also in cerebral spinal fluid (CSF) from people with AD, (Wang et al., 2015) indicating that lack of SPMs might result in failure of the resolution cascade of inflammation. Particularly, by regulating microglial functions and responses, SPMs seem to be able to suppress chronic neuroinflammation (Laye et al., 2018; Lee et al., 2020). Thus, failure of a normal pro-inflammatory immune response to resolve may lead to persistent central inflammation that contributes to unsuccessful clearance of Aβ plaques as they form, neuronal death, and ultimately cognitive decline. Individual metabolic, and dietary (lipid) profiles can disrupt the appropriate PUFA profile and therefore SPM production and contribute to this process. Here, we integrate evidence for the interface between these factors, and how they contribute to a pro-inflammatory brain milieu.

The close interaction between lipid metabolism and inflammation with aging is known to be exacerbated by poor nutrition at any life stage and plays a pivotal role in neurodegenerative diseases (Komleva et al., 2020). Thus, metabolic sensors such as adipokines, bioactive factors secreted from adipose tissue, are important neuroimmune mediators in obesity and aging (Rummel et al., 2010; Koenig et al., 2014). In this regard, we now know that obesity throughout life and overfeeding in the early perinatal period affects circulating inflammatory factors and adipokines long-term, (Yam et al., 2017) contributing to persistent central inflammation and worsened "inflammaging", (Hoeijmakers et al., 2017) the low-grade pro-inflammatory state that develops with aging. Inflammaging can also be stimulated by non-dietary inflammatory factors and exposure of murine models of AD to non-dietary adversity in the form of stress, particularly during early development, induces an altered neuroinflammatory response and aggravated amyloid pathology that develops in an age-dependent manner (Hoeijmakers et al., 2017; Lesuis et al., 2019). In the field, however, there is currently no clear understanding of how these inflammatory processes cause AD neuropathology and cognitive decline. Recent clinical trials showed that anti-Aβ monoclonal antibodies lecanemab and donanemab can improve cognition and key AD biomarkers, but their effects on inflammation remain unknown (van Dyck et al., 2023; Sims et al., 2023). Here we will explore existing literature on AD-like sequelae of several neuroinflammatory processes and discuss consideration of dietary and life-experience risk factors for the disease as well as implications for the research field. We focus here on the inflammatory effects of aging, as the major risk factor for sporadic AD and lipid metabolism as a contributor and potential target for manipulation. We particularly consider the effects of early life lifestyle challenges, including dietary and stress, because of the notable vulnerability of the developing brain. This is a narrative review, so systematic guidelines were not needed nor followed, but we included English-language articles indexed in Pubmed that addressed the association between AD and lipids, aging, metabolism, early life adversities and sex differences.

2. Alzheimer's disease and lipids

The intricate interactions between neurons and immune cells are crucial to brain homeostasis and the disturbance of these delicate interactions is now well-recognized as a high-risk factor for neurodegenerative diseases (reviewed in (Hammond et al., 2019)). As a result, the pro-inflammatory environment that develops during aging contributes to brain vulnerability to the development of cognitive decline, dementia and AD (Cunningham and Hennessy, 2015). In addition to peripheral inflammation contributing to the neurodegenerative process, inflammation occurring directly in the brain is a key driver, and microglia, resident brain immune cells highly suspected to contribute to AD, are crucially involved in this (Villeda et al., 2014; Sarlus and Heneka, 2017). Recent attention has been directed towards lipids in the complex interplay between microglia and AD (Shippy and Ulland, 2023; Garcia-Segura et al., 2023; Paasila et al., 2021; Yang et al., 2020a).

With a significant presence of over 50% in the total dry weight of a typical brain, lipids play a vital and indispensable role in the brain's physiology, actively contributing to its structure and function. The main lipids found in the brain are glycerophospholipids, sphingolipids, and cholesterol (Hamilton et al., 2007). They fulfill critical functions in glial and neuronal activity, structural maturation, and serve as essential energy reserves. Although lipidomic studies have unveiled alterations in various lipid species in the brains of AD patients, a considerable portion of research has been dedicated to understanding the impact of changes in cholesterol, PUFAs, and phospholipids on neurodegenerative processes (Saher, 2023; Husain et al., 2021). The dysregulation of lipid metabolism, especially concerning cholesterol, PUFAs, and phospholipids, is strongly linked to neuroinflammatory processes and plays a significant role in the onset, development and progression of AD (Hansen and Wang, 2023; Yin, 2023). They have particularly been shown to be involved in the relationship between neurons and brain immune cells such as microglia (Laye et al., 2018; Joffre et al., 2020). In addition, the observation that polymorphisms of genes involved in lipid metabolism and neuroinflammatory processes are significant risk factors for AD, reinforces the potential role of these lipid metabolism alterations in the pathogenesis of the disease. As an example, recent data have shed light on the intricate relationship between lipids, triggering receptor expressed on myeloid cells 2 (TREM2), and AD pathogenesis in humans. TREM2 binds to phospholipids, high- and low-density lipoproteins (LDL), lipids found in apoptotic neurons, and apolipoprotein E (ApoE), a crucial lipid transporter in the brain. Importantly for AD, TREM2 exhibits the ability to interact with a diverse range of pathological

molecules implicated in AD, including APOE and Aβ (Atagi et al., 2015). In addition, this lipid receptor alters cholesterol metabolism in the brain, which is abnormally high in AD. Interestingly, TREM2 is exclusively expressed on microglia in the brain and macrophages in the periphery and regulates immune and phagocytic activities of these cells (Nugent et al., 2020). TREM2 stands out as the most potent immune-specific genetic susceptibility determinant for AD, with specific variants conferring a notable three-to-four-fold elevation in the risk of developing the disease (Guerreiro et al., 2013). As a result, TREM2 gene variants are associated with an increased risk of developing AD through their contribution to AD pathogenesis, including neuroinflammatory processes, microglia-dependent clearance of amyloid deposits, and lipid droplet formation (Colonna and Wang, 2016; Krasemann et al., 2017). In terms of animal models targeting TREM2 or its single nucleotide polymorphisms (SNPs) in AD, some interesting results have been generated. The deletion of TREM2 has been found to initially decrease amyloid deposition. Microglial TREM2 deficiency is linked to defective signaling of mammalian target of rapamycin (mTOR), which increases autophagy and reduces amyloid deposition in the short term by weakening the microglial inflammatory response. However, dysfunctional mTOR signaling has deleterious long-term effects, impeding the microglia's capacity to respond to amyloid accumulation across time. Therefore, it paradoxically promotes amyloid deposition at later stages of AD, (Jay et al., 2017; Ulland et al., 2017) in accordance with studies demonstrating that the reduction in microglial phagocytosis of Aβ leads to a decrease in dense core plaque pathology (Huang et al., 2021) and depletion of the microglial cell population can lead to accumulation of Aβ plaques (Clayton et al., 2021). However, depleting microglia in AD mouse models reduces synaptic and neuronal loss, ultimately improving cognition, (Spangenberg et al., 2016) and reduces tau-associated neurodegeneration (Shi et al., 2019; Asai et al., 2015). In addition to TREM2, other glial lipid metabolism genes such as *APOEε4*, are AD risk factors, (Karch and Goate, 2015; Claes et al., 2021) further reinforcing the role of lipids in AD pathogenesis. The presence of this allele accelerates hippocampal volume loss and tau burden in human brains and mouse models of AD. Additionally, *APOEε4* enhances neuroinflammation and gliosis and is associated with reduced myelination and white matter integrity. APOE is mainly expressed by astrocytes, but *APOEε4* expressed by neurons (Koutsodendris et al., 2023) and microglia (Shi et al., 2019) is important to AD pathology. Recently, studies have also unveiled the intricate interaction between APOE and TREM2, (Gratuze et al., 2023) further emphasizing the critical importance of better comprehending the relationship between lipid metabolism, neuroinflammation, and the pathogenesis of AD.

Other bioactive lipids have been reported to be involved in AD pathological mechanisms, particularly neuroinflammatory processes. Recent data pinpoint that cognitive decline triggered by age-associated inflammation involves specific lipids (Minhas et al., 2021). In particular, PUFAs from the n-6 and n-3 families and their derivatives, so-called oxylipins, are important regulators of inflammation, both in the periphery and brain (Laye et al., 2018). PUFAs consist of two main series, n-3 and n-6. The long chain (LC) n-3 series includes eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), which are derived from the essential nutrient α-linolenic acid (ALA; 18:3n-3). Conversely, the LC n-6 series includes arachidonic acid (ARA; 20:4n-6), synthesized from the essential nutrient linoleic acid (LA; 18:2n-6) (Bazinet and Laye, 2014). Mammals are able to synthesize both LC n-3 and n-6 PUFAs from ALA and LA plant sources through a series of enzymatic reactions involving desaturases (delta5 and 6), elongases (ELOVL2 and 5), and partial peroxisomal β-oxidation. The main fatty acid desaturase (FADS) and ELOVL activities occur in the liver, while are low in the brain (Valenzuela et al., 2024). Importantly, ALA and LA compete for the same enzymatic machinery leading to altered levels of LC n-3 and n-6 PUFA in tissue in the case of an imbalance in LNA and LA (Videla et al., 2022). It is important to note that females have higher blood levels of DHA than males, which is linked to a higher conversion rate of ALA in DHA. In addition, EPA is also an important source of DHA in females, which could be linked to an ELOVL2 SNP carried by females. ARA, EPA and DHA are also directly provided to mammals by different animal dietary sources that influence LC PUFA blood levels in addition to desaturase and elongase SNPs (Valenzuela et al., 2024). Other nutritional factors, among those with antioxidant activities influence desaturase and ELOVL activities (Videla et al., 2022) and disease conditions affecting sugar metabolism and sensitivity (e.g. diabetes) or liver functions (e.g. non-alcoholic fatty liver disease) influence PUFA metabolism and LC PUFA levels (Videla et al., 2022).

PUFAs are very abundant in the brain and are esterified in the membrane phospholipids of neurons and glial cells, including microglial cells (Laye et al., 2018; Bazinet and Laye, 2014). Decreased levels of n-3 PUFAs have been reported in the blood and the brain of aged subjects with cognitive decline and patients diagnosed with neurological disorders such as AD, although not all studies are in agreement on this (Plourde et al., 2007; Ooi et al., 2021; Cisbani and Bazinet, 2021). N-3 PUFA-derived SPMs (resolvins, maresins and protectins) are crucial not only to the resolution of inflammation but also to the enhancement of tissue restoration tissue restoration, (Hellmann et al., 2018; Zhang et al., 2016; Buckley et al., 2014) including in the brain (Laye et al., 2018; Belayev et al., 2018; Pu et al., 2013). Interestingly, SPM levels are also decreased in the brain and CSF of patients with mild cognitive impairment and AD, (Wang et al., 2015; Do et al., 2023) and in 5xFAD mice (Kantarci et al., 2018). In addition, recent data revealed that intranasal pro-resolving SPM administration to a knock-in mouse model of AD (AppNL-G-F/NL-G-F) improves memory deficits and neuroinflammation (Emre et al., 2022) as does intraperitoneal resolvin E1 and lipoxin in the 5xFAD mice, (Kantarci et al., 2018) reinforcing the idea that these PUFA-derivatives could be used as a therapeutic strategy to slow AD-associated neuroinflammatory processes. However, despite the potential for SPMs as an exciting new avenue for treating AD-associated neuroinflammation, further, more expansive, studies are needed to demonstrate their ability to target neuroinflammatory processes, as well as brain immune cells like microglia and astrocytes involved in this process. Recently, controversies have emerged on the detection and exact enzymatic pathways for SPM production in biological samples. In particular, resolvins are potent but unstable lipid mediators, which may be rapidly converted into inactive products and, therefore, are difficult to detect. Thus, further improvement and harmonization of the analytical methods is warranted for evaluation of SPMs as biomarkers for disease states in patients and for evaluation of functional phenotypes such as pro- or anti-inflammatory states of astrocytes and microglia in the brain or immune cells in the peripheral blood (Schebb et al., 2022; Sinha, 2022). In addition to PUFAs, other dietary supplements such as resveratrol, curcumin, and quercetin, acting through antioxidant, anti-inflammatory, and sirtuin-activating mechanisms, can also influence SPMs and contribute to the resolution of neuroinflammation, suggesting a broader scope for nutraceutical interventions in managing neurodegenerative diseases. These, too, need further investigation.

3. Aging as a risk factor for AD

Aging remains the major risk factor for dementia and neurodegenerative disorders. Aging is a complex process and exhibits a strong connection to gradual increases in chronic and systemic inflammation due to an imbalance of pro- and anti-inflammatory mechanisms (Calabrese et al., 2018). This low-grade condition is called "inflammaging" and is primarily accompanied by elevated levels of pro-inflammatory cytokines like interleukin (IL)-6 and acute phase proteins such as C-reactive protein (CRP) in an age-dependent manner; as previously shown for humans and animals (Wei et al., 1992; Ershler et al., 1993; Puzianowska-Kuznicka et al., 2016). The age-based increase in IL-6 is observed not only in healthy aging individuals, but also in adults who develop different diseases and disabilities related to aging such as cardiovascular diseases, stroke, type 2 diabetes, cancer and dementia

(Puzianowska-Kuznicka et al., 2016). Overall, healthy aging individuals have lower concentrations of IL-6 and CRP than elderly persons who have any diseases (Puzianowska-Kuznicka et al., 2016). As reviewed by Calabrese et al. (2018), (Calabrese et al., 2018) while centenarians, i.e. those who survive to very old age, seem to have a good balance between pro- and anti-inflammatory processes, the absence of adequate anti-inflammatory networks can intensify processes related to inflammaging (Calabrese et al., 2018). Accordingly, healthy aging and longevity are not only based on a reduced predisposition to pro-inflammatory insults, but also greatly depend on a functional anti-inflammatory system (Franceschi et al., 2007). Moreover, an increase in IL-6 and CRP is related to poorer physical and cognitive performance at older age (Puzianowska-Kuznicka et al., 2016) as well as worse global cognition, executive functions and processing speed (Schram et al., 2007; Tegeler et al., 2016). Higher levels of IL-6 and CRP also seem to be capable of predicting cognitive decline and dementia in older adults at 3–7 years follow up, (Bradburn et al., 2017; Kuo et al., 2005) with longitudinal follow up measurements being essential to make sense of these data. Due to the close linkage between advanced age and increased systemic inflammation, aging is one of the major risk factors for development of neurodegeneration and related pathologies including AD. Indeed, cross-species analysis of healthy aging and health-span similarly indicates a conserved relationship to inflammation, lipids, and autophagy (Moller et al., 2020, 2022).

Neuroinflammation plays a key role in various neurodegenerative diseases (Ransohoff, 2016; Leng and Edison, 2021; Lempriere, 2023) and by enhancing glial pro-inflammatory activity and exacerbating aberrant neuronal signalling through deleterious neuroinflammatory responses, aging might deteriorate the microenvironment within the CNS and contribute to progression of cognitive dysfunction (Kumar, 2018). Nonetheless, there is presently limited knowledge about the detailed pathophysiological mechanisms related to inflammaging. Interestingly, some studies suggest that Aβ deposition and accumulation of neurofibrillary tangles (NFTs) in AD mouse models are strongly associated with cellular senescence within the brain (Moller et al., 2022; Wei et al., 2016; Musi et al., 2018). Cellular senescence is accompanied by alterations in numerous signalling mechanisms that impede cell survival and cell cycle propagation including mitogen-activated protein kinases, phosphoinositide 3-kinases, and mTOR (Kumari and Jat, 2021). In this context, Zhang et al. (2019) demonstrated that removal of senescent cells in AD mice through the use of senolytics leads to curtailed neuroinflammation, minimised burden of Aβ plaques, and improvement in cognitive impairments, (Zhang et al., 2019) indicating that senescence of cells aggravates AD-linked pathologies and plays a crucial role in the pathophysiology of AD.

4. Interactions between aging, metabolism, and inflammation in AD

Based on demographic changes and elevated human longevity, aging is also increasingly associated with higher susceptibility to chronic diseases, including complications from age-related obesity in the elderly. The prevalence of obesity has dramatically increased among all age groups over the past decades, already gaining epidemic proportions, and is correlated with development of the most frequent age-related diseases like diabetes, osteoarthritis and cognitive dysfunction (Frasca et al., 2017; Gratal et al., 2020). In addition, obesity has been shown to drastically promote chronic low-grade inflammation, potentially accelerating inflammaging. As such, circulating immune modulators are elevated in obese individuals, resulting in higher vulnerability to comorbidities like cardiovascular impairments, diabetes and psychoneuropathologies (Koenig et al., 2014; Aguilar-Valles et al., 2015). Many of these bioactive modulators, jointly known as adipokines and adipocytokines, originate directly from white adipose tissue (Aguilar-Valles et al., 2015). They include adipokines like leptin and adiponectin; cytokines such as IL-1β, tumor necrosis factor (TNF); chemokines, complement factors, such as adipsin; and hormones (e.g. leptin and adiponectin) (Neumann et al., 2021). The quantity of adipokines produced and released is proportional to the increasing tissue mass during obesity (Aguilar-Valles et al., 2015). Metabolic disorders related to obesity can trigger low-grade chronic inflammation, named "metainflammation" (Gratal et al., 2020). Major depressive disorder is similarly a multimorbid condition for obesity, dementia, and AD, with hypothetically common roots in metabolic syndrome and low-grade inflammation (Marx et al., 2017). The onset of obesity is often accompanied by an increased amount of senescent cells present in adipose tissue and other parts of the body (Chaib et al., 2022). The higher proportion of adipocytes in the elderly finally results in altered secretion patterns causing a chronic inflammatory milieu linked to local and systemic dysfunction (Chaib et al., 2022). Interestingly, Chaib et al. (2022) have recently reviewed current evidence that the removal of aged cells by the use of senolytics may result in delayed, prohibited or eased dysfunction of organs impacted by obesity (Chaib et al., 2022). In addition, not only alterations in composition and metabolism but also modified distribution of adipose tissue within the aging body might be components of a vicious cycle that accelerates aging and contributes to the onset of various age-related diseases, (Jura and Kozak, 2016) potentially including neurodegeneration during AD. Age-related visceral obesity may also increase the risk for AD and accelerate its onset and promote its progression due to initiation of insulin resistance, dysregulation of adipocytokines resulting in hypoadiponectinemia, leptin resistance and activation of various pro-inflammatory signalling pathways (Al-Kuraishy et al., 2023).

Notably, the strongly connected effects between aging, metabolism and inflammation can be deteriorated by poor nutrition at any stage of life indicating a pivotal role of metainflammation, especially in the context of neurodegenerative diseases (Komleva et al., 2020). Various studies have revealed evidence that metabolic sensors like adipokines exhibit important neuroimmune functions related to obesity and aging (Rummel et al., 2010; Koenig et al., 2014). Particularly the appetite-suppressing adipokine leptin seems to play a key role in modulating neuroinflammation by increasing leukocyte recruitment into the brain and elevating the amount of pro-inflammatory cytokines and chemokines in the CNS-microenvironment as shown by Rummel et al. (2010) in an experimental study after lipopolysaccharide (LPS)-treatment in mice (Rummel et al., 2010; Aguilar-Valles et al., 2015). Koenig et al. (2014) have revealed that treatment of rats at different ages with neutralizing leptin antiserum may lead to debilitated LPS-induced febrile responses, a hallmark of systemic inflammation, with age-related obesity contributing to modulation of the inflammatory response (Koenig et al., 2014). Moreover, leptin can potentiate microglial responses to LPS by altering the morphology and activity of rat microglia in primary cell cultures (Lafrance et al., 2010). However, others have revealed that leptin may also facilitate neurogenic processes as well as attenuate Aβ-related neurodegeneration and, therefore, can alleviate disease states in the double transgenic APPswe/PS1dE9 (2xTgAD) mouse model of AD (Calio et al., 2021). After chronic peripheral administration in Tg2576 mice, Fewlass et al. (2004) reported the striking ability of leptin to directly decrease the Aβ-load within the brain (Fewlass et al., 2004). In addition, leptin deficiency and the associated hypothermia may exacerbate tau hyperphosphorylation at numerous tau phospho-epitopes, as shown in ob/ob mice (Gratuze et al., 2017). By affecting NMDA receptor function, leptin also promotes synaptic plasticity in the hippocampus as revealed in hippocampal cultures and slices from rats (Shanley et al., 2001). Lilamand et al. (2023) demonstrated that decreased plasma leptin levels are significantly linked not only to Aβ concentrations in CSF but also to AD diagnosis validated through analyses of CSF biomarkers (Lilamand et al., 2023). Overall, it is been suggested that long-term sufficient levels of leptin have a (neuro)protective role in AD (Marwarha and Ghribi, 2012).

Adipokines such as C1q/TNF-related protein 3 (CTRP3) have also emerged as anti-inflammatory modulators for microglial cells during

LPS-induced inflammation (Meng et al., 2019). These may efficiently protect against pro-inflammatory states such as during sevoflurane anaesthesia-induced post-operative cognitive dysfunction as shown in CTRP3-overexpressed aged rats (Yang et al., 2020b). Levels of CTRP3 decrease with obesity, (Wolf et al., 2015) can be increased by certain forms of aerobic exercise training (Hasegawa et al., 2018) and are altered by gender (Wagner et al., 2016). A potential role for CTRP3 in AD remains to be explored in the future, but Hong et al. have shown that inhibition of C1q, C3, or the microglial complement receptor, CR3, reduces phagocytic microglia and synapse loss (Hong et al., 2016).

The increased risk of mortality in obesity is strongly determined by metabolic health and nutrition, (Ahima and Lazar, 2013) for example, by the balance of n-3 to n-6 PUFAs, the optimisation of which can improve memory performance in aged mice (Joffre et al., 2020; Chataigner et al., 2021). Some adipokines, like adiponectin, for instance, have been shown to increase in human plasma after supplementation with linoleic acid-rich vegetable oil, and this is accompanied by higher production of SPMs including the docohexaenoic acid (DHA)-oxylipin, 12,20-dihydroxydocosapentaenoic acid (DiHDoPA) (Cole et al., 2020). Recently, precursors of the metabolite DiHDoPA have been shown to exhibit neurogenic and anti-apoptotic effects in a human hippocampal progenitor cell line and are associated with protective effects of n-3 PUFA supplementation (Borsini et al., 2021). Such findings link the effects of adipokines to protective properties that have been shown for SPMs such as Resolvin D1, which can improve amyloid phagocytosis and decrease amyloid toxicity *in vitro (*Zhu et al., 2016*)*. The connection between adipokines and SPMs may even be bidirectional. There is evidence that Resolvin D1 and D2 can elevate expression and secretion patterns of adiponectin within adipose tissue explants from obese mice (Claria et al., 2012). Such effects may be overall related to the ability of some SPMs to increase adiponectin expression via peroxisome-proliferator activated receptor γ related mechanisms (Choi et al., 2005; Gart et al., 2021).

These confounding factors of obesity and aging need to be considered when using animal models to investigate AD. While some rodent models do exclude the influence of obesity and aging since they are based in young and lean animals, further complexity should be considered if extrapolating such evidence to the human situation among many other factors in regard to age, nutrition and obesity. This consideration also applies in the other direction; some animal models do depend on the aging phenotype to develop AD-related symptomatology and pathophysiological features observed in human AD post-mortem brains. As such, transgenic models focussing on the Aβ hypothesis report pathologies appearing in an age range of 2–24 months. It also must be stressed that the age of appearance of AD-like pathologies can vary from laboratory to laboratory depending upon a host of environmental variables. Further experimental studies focussing on the intimate interplay of age, nutrition and obesity are, therefore, needed for studying models of neurodegenerative disorders like AD.

5. The role of early life adversity in the pathogenesis of AD

While proximal causes including lipid balance, biological age, inflammatory profiles (and genetics) can help to quantify the risk of AD and its development, it is increasingly being recognized that the foundations for functioning of the brain in later life are laid down early in life (Short and Baram, 2019; Van den Bergh et al., 2020). The developing brain is highly vulnerable to environmental factors and consequently an adverse environment during pregnancy and childhood may hamper brain development, with long lasting effects on brain structure and function and potentially the risk for AD in older age. A recent systematic review including 68 studies examining the role of prenatal factors in dementia concluded that particularly factors related to a suboptimal prenatal environment were associated with an increased dementia risk (Wiegersma et al., 2023). As noted in this review, though, studying a late life outcome after a prenatal exposure is challenging given the long stretch of time between exposure and outcome. Therefore, many studies in this field have relied on retrospective data or have used indirect measures of exposure to adverse prenatal factors, such as birth weight. A unique study in this respect is the Dutch famine birth cohort study (De Rooij et al., 2022). The quasi-experimental design of this study provides a unique opportunity to investigate effects of undernutrition in pregnancy that would not be ethically possible to examine otherwise. The long period of follow-up allows for unusually long-term consequences to be investigated decades after the exposure of interest. Thus, exposure to the Dutch 1944–1945 famine during early gestation is associated with poorer cognitive function, smaller brain volumes, worse brain perfusion, higher BrainAGE and a resting state activity pattern of network desegregation fitting with brain aging in men (De Rooij et al., 2022; Boots et al., 2022). A similar study investigated prenatal exposure to the great Chinese famine and found this to be associated with a higher prevalence of dementia (Kang et al., 2017). Adversity during childhood years has been linked to a higher risk for AD by several studies (as reviewed in (Huang et al., 2023)). Different types of early life adversities during childhood, including parental death, trauma exposure and living in custody or an orphanage, all confer an increased risk of developing dementia and AD (Huang et al., 2023). This observational evidence has been corroborated by findings in animal models, particularly in rodent models of early life adversity (Lesuis et al., 2018; Hoeijmakers et al., 2018). Early life adversity exposure in predictable transgenic mice (APP/PS1) aggravates Aβ pathology and impairments in cognitive flexibility and memory (Hoeijmakers et al., 2017; Lesuis et al., 2018; Hui et al., 2017) as well as impact on the neuroimmune system (Hoeijmakers et al., 2017; Abbink et al., 2020). Emphasizing the role of neuroimmune and lipid dysregulation as key emerging hallmarks of AD, (Hoeijmakers et al., 2016) early life adversity, including early life poor diet or stress, has been demonstrated to prime microglia, (De Luca et al., 2016; Reemst et al., 2022) to increase the neuroimmune response to amyloid accumulation, (Hoeijmakers et al., 2017) and to impair brain lipids, for example, n-3 PUFAs and their derivatives (Reemst et al., 2022; Yam et al., 2019) in the long-term, resulting in lipid dis-homeostasis. Interestingly, an early n-3 PUFA-enriched diet was able to protect against the early life adversity-induced cognitive deficits and the associated neuroimmune alterations, pointing towards potential early departure points for prevention and intervention (Yam et al., 2019).

6. Sex differences in AD

Lipid, metabolic, and neuroinflammatory profiles are clearly key contributors to AD. In addition, life experience, particularly during vulnerable programming stages, can influence the balance of these profiles. However, biological sex plays into this mix as well (Zhao et al., 2016; Ferretti et al., 2018). Women are twice as likely to develop AD than men, and nearly two thirds of the current cases of AD are in women, at least in some geographical regions (Hudomiet et al., 2022; Chene et al., 2015). Although one of the potential reasons for female bias in the lifetime risk of AD is the greater life expectancy of women, (Chene et al., 2015) age-adjusted prevalence of AD is still higher among women, than men (Hudomiet et al., 2022). While some studies suggest the incidence of AD does not significantly differ between men and women, there is a general consensus that AD affects both genders in many different ways and that sex and gender differences that affect the risk to develop AD are likely to depend on the geographical region and the timeframe of observations (Mielke et al., 2018; Aggarwal and Mielke, 2023). Therefore, the study of sex/gender differences in AD is critical with the aim to identify the underlying biological mechanisms that may be unique for each.

Hormonal changes, and particularly the drop in estrogen levels driven by the cessation of ovulatory cycles at menopause, are one of the important contributors to the development of neurodegenerative disease (Zarate et al., 2017). In particular, estrogen is shown to increase clearance of Aβ, reduce pro-inflammatory cytokines secretion, and

downregulate the inflammatory nuclear factor (NF)-κB pathway (Mishra et al., 2023). Earlier onset of menopause is associated with higher risk of cognitive decline and AD neuropathology, particularly neuritic plaques (Bove et al., 2014). Additional evidence suggests that female *APOEε4* carriers have an increased risk of developing AD at younger ages (65–75 years) compared to male carriers (Neu et al., 2017). This age-specific effect of *APOEε4* carriage could be driven by menopause-related hormonal changes preceding this age of increased vulnerability (Riedel et al., 2016). Notable sex differences in AD pathology (including the number of neuritic plaques, diffuse plaques and NFTs) have also been shown, with increased AD pathology in women compared to men (Barnes et al., 2005).

Despite the critical need for understanding gender differences in AD risk and disease progression, sex has not been sufficiently considered in preclinical models of AD (Waters, 2021). Nevertheless, notable sex differences have been observed in some preclinical studies, particularly with the 3xTg-AD line, (Dennison et al., 2021; Bories et al., 2012; Clinton et al., 2007; Hirata-Fukae et al., 2008) including reports of earlier glucose intolerance and cortical amyloid pathology in females (Vandal et al., 2015). In the APP/PS1, APP/PS1dE9 and Tg2576 models, increased Aβ load has been shown in females (Callahan et al., 2001; Ordonez-Gutierrez et al., 2015; Li et al., 2016; Schmid et al., 2019). In terms of cognitive parameters, female Tg2576 mice have impaired reference memory, (Schmid et al., 2019) and 5xFAD females exhibit enhanced sensitivity of hippocampal AD-related pathological measures to the effects of stress, compared to their male counterparts (Devi et al., 2010). 3xTg-AD females also show an elevated corticosterone response to stress compared to males, particularly at younger ages, with subsequent detrimental effects on their cognitive performance (Clinton et al., 2007). In mice that express the human *APOEε4* allele, only females show impairments in spatial and avoidance memory tasks (Bour et al., 2008). Complicating the picture, ε4FAD mice, generated by crossing 5xFAD to mice carrying the human *APOEε4* allele exhibit an opposite sex bias to that seen in clinical studies in AD cerebrovascular pathology. In humans, cerebral microbleeds are more common in men than women with AD, while microbleeds are increased in ε4FAD female mice, compared to male mice (Cacciottolo et al., 2016).

Overall, it appears that while some sex differences in animal models of AD reproduce the sexual dimorphism seen clinically, others do not correlate or contradict clinical evidence. Such disparate findings need to be accounted for in the interpretation of animal studies. Testing environments should also be optimised for females as well as males and the possibility considered that apparent sex differences could relate to testing optimisation or cognitive strategies rather than to real deficits in one sex over the other, as has been shown for different rodent strains (Weitzner et al., 2015). It is also important to point out the difficulty in reproducing the gradual effects of menopause-related hormonal changes on neurodegeneration and cognitive decline in rodents. Nevertheless, improved understanding of sex differences in AD is critical for the development of prevention and treatment strategies, and as such should be an integral component of both clinical and preclinical studies, particularly with respect to drug development and establishment of safety and efficacy data. In addition to assessing the sex-dependent mechanisms in AD neuropathology and disease manifestation, it is also important to understand the sexual dimorphism of risk factors of AD, including any inflammatory and metabolic imbalance. In particular, females are more prone to inflammation (Klein and Flanagan, 2016) and have an increased risk of overweight and obesity, compared to males, (Cooper et al., 2021) but are less susceptible to the long-term effects of early life poor diet (Ziko et al., 2017). In addition to being genetically or hormonally driven, early life environmental factors can influence the emergence of sex/gender differences in disease susceptibility, including neurodegeneration (Mak et al., 2021; Morrow, 2015). Whether predisposition to AD is modulated by early life adversity in a sex or gender-dependent manner requires further investigation.

7. Discussion

Neuroinflammation (driven by the brain's primary immune cells, microglia) has been increasingly acknowledged as an important player in AD pathology. Emerging research suggests that early life adversity primes microglia, rendering them more sensitive to subsequent challenges. In addition, PUFAs and their derivatives play a key role in modulating microglia. N-3 PUFA metabolism is altered by early life adversity and derivatives of n-3 PUFAs (SPMs), have been found to be altered in post-mortem AD brains. Inflammation and metabolism are also tightly connected in the context of early life adversity and AD. Together these data suggest an intricate interplay between early life experiences, the aging process, neuroinflammation, and diet. With biological sex thrown into the mix, it is unsurprising that our current understanding of AD lacks the nuance needed for successful treatment development (Fig. 1).

In parallel with the recent development of biomarkers for tau and Aβ pathologies, imaging and fluid biomarkers to assess neuroinflammation in the course of AD progression are urgently needed (Simren et al., 2023; Bieger et al., 2023; Fontana et al., 2023). These considerations also highlight the need for more personalised treatments for AD and personalised trials for new therapies in light of the individual's lipid and neuroinflammatory profiles. As such, one reason for the failure of n-3 supplementation to ameliorate AD on a population basis in many studies (Vauzour et al., 2023) may be because it is not beneficial except in cases of an existing PUFA imbalance. Notably, the interaction of PUFAs with other factors to reduce AD risk is being discussed in the literature. For example, the risk of AD is reduced if PUFAs are given vitamin B, and the beneficial effects on brain atrophy in AD and cognitive performance in mild cognitive impairment are only observed in those with high blood levels of PUFA or n-3 (Jernerén et al., 2015; Oulhaj et al., 2016). Association studies on the interaction between the APOE protein and PUFAs have produced contradictory results, with some studies suggesting a decreased risk of AD in *APOEε4* carriers when treated with PUFA-enriched food, (Laitinen et al., 2006; Kivipelto et al., 2008) while other studies suggesting the non-carriers of *APOEε4* have a reduced risk while carriers have no effect (Huang et al., 2005; Barberger-Gateau et al., 2007). These results, although in need of replication, (Chang et al., 2024; Fairbairn et al., 2023; Barberger-Gateau et al., 2011) highlight the importance of considering multiple factors that could possibly alter the outcomes of intervention studies conducted on large populations with uncontrolled multiple variables.

Astrocytes perform multiple integral functions in maintenance of homeostasis, maintenance and repair of the blood-brain barrier, supply of neurons with pivotal metabolites and growth factors as well as the development and plasticity of synapses and, therefore, are important contributors to a healthy CNS (Patani et al., 2023). Besides this huge variety of essential physiological functions, astrocytes also play a key role in the pathogenesis of AD (Patani et al., 2023; Chun and Lee, 2018). By adapting their phenotype and downregulating supportive purposes, astrocytes can (similar to microglia) respond to certain pathophysiological circumstances (e.g., high Aβ load, release of proinflammatory cytokines by activated microglia) and become "reactive astrocytes", which promote neuroinflammation through the secretion of neurotoxic factors such as components of the complement system (e.g., C3) and chemokines (e.g., MCP-1, MIP-1α, IP-10) (Singh, 2022; Lawrence et al., 2023; Liu et al., 2014). However, there is also evidence that reactive astrocytes are capable of binding, internalizing and degrading deposited Aβ, indicating a neuroprotective role for astrocytes in AD, (Wyss-Coray et al., 2003) which might be fostered by the interaction with microglia (Rostami et al., 2021). Recent reviews on this topic include (Singh, 2022; Fakhoury, 2018). In APP/PS1 mice, inactivation of prominent indicators of reactive astrocytes like glial fibrillary acidic protein (GFAP) and vimentin (Kamphuis et al., 2015) leads to an increased Aβ deposition, suggesting that astrocytic activation limits plaque expansion (Kraft et al., 2013). Interestingly, genetic n-3 enrichment in combination with

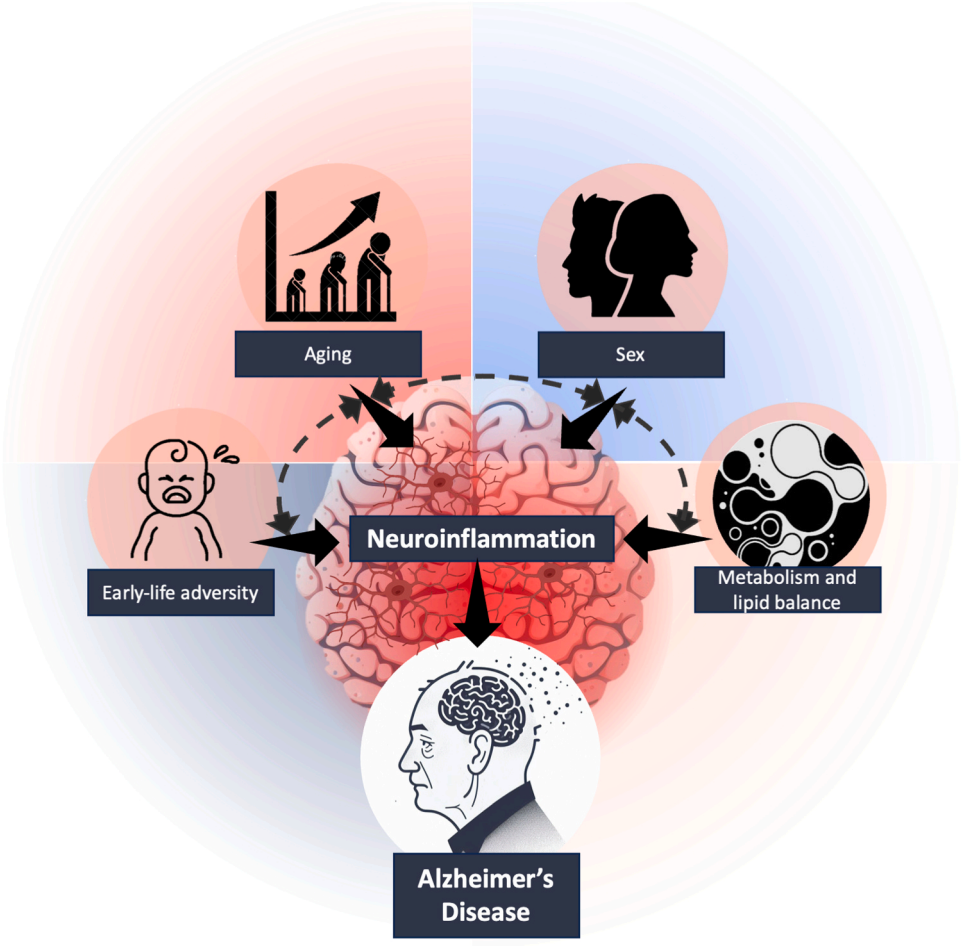

Fig. 1. The interplay between neuroinflammation, aging, gender, metabolism and lipid balance, and early life experience serve to determine predisposition to Alzheimer's disease (additional factors such as genetics are not discussed here). This image was created with the assistance of DALL·E 2 Open AI and BioRender.com; Toronto, Canada.

resolvin receptor deficiency also has beneficial impact on the expression of GFAP and, thus, might enhance the recruitment of reactive astrocytes (Hernandez et al., 2023). Moreover, a recent systematic review and meta-analysis even discussed plasma GFAP as a potential biomarker in AD (Kim et al., 2023; Cicognola et al., 2021; Chatterjee et al., 2021). However, while the potential relevance of GFAP as a biomarker for secondary prevention of AD is promising, there are currently a number of laboratory processing factors that influence the validity of this measure, and further assessments in population-based cohort studies are required (Ashton et al., 2021).

There is a clear need for a greater understanding of which combination of inflammatory and metabolic sensors contribute to neurodegeneration, how production of SPMs can be stimulated to reverse these effects, and how life events, whether prenatal, in childhood, or in the aging period can dictate our AD risk. Nonetheless, the current investigation into lipid balance as a nuanced contributor to AD raises the possibility that strategic dietary interventions on an individualised basis may be beneficial for some with the disease; a possibility that needs urgent further investigation. In addition to potential dietary interventions, there are various avenues for harm minimization that we can consider. As discussed throughout, an unhealthy lifestyle is associated with increased risk of neuroinflammation and increased risk of developing AD. In addition to poor nutrition, obesity, and stress, smoking, sleep deprivation, and heavy alcohol use are associated with increased risk of neuroinflammation, increased oxidative stress, increased neurodegeneration, and AD (Cataldo et al., 2010; Zhong et al., 2015; Alrouji et al., 2019; Sadeghmousavi et al., 2020; Lucey, 2020; Rehm et al., 2019; Lowe et al., 2020). Nutrient deficiencies and imbalances may also increase the AD and neuroinflammatory risk, not least PUFA imbalance as discussed here (Barberger-Gateau et al., 2007; Rivers-Auty et al., 2021). Psychological conditions such as depression and PTSD may also increase the risk of neuroinflammation and AD (Saiz-Vazquez et al., 2021; Yaffe et al., 2010; Zhou et al., 2022; Lee et al., 2022). Therefore, maintaining a healthy, stress-free lifestyle may be an important preventative strategy against neuroinflammation and AD. In addition to dietary changes that could prevent or alleviate neuroinflammation, (Tarini Shankar et al., 2020) emphasis on other interventions such as physical activity (Wang et al., 2023) and social engagement (Walker et al., 2019) is critical for improving cognitive health and mental wellbeing in the elderly.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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