Sex-Specific Differences in Alzheimer's Disease

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Alzheimer's Disease (AD) is a prevalent neurodegenerative disorder that affects millions of patients worldwide. AD risk and the disease itself vary for patients on the basis of their biological sex. This divergence is partially attributed to differing microglial gene expression, chromosomal variance, and alternate risk factors, which result in variance in AD risk and resilience. The pathological accumulation of notable AD hallmarks, including Aβ plaques, tau tangles, and iron accumulation in the brain, also varies with sex and contributes to disease severity. AD patients exhibit sex-specific differences in neuropsychiatric and behavioral symptoms as well, warranting sex-specific preclinical and clinical research on AD onset, progression, and treatment.

Introduction

As the most widespread type of dementia, Alzheimer's Disease (AD) is expected to have impacted approximately 13.8 million people in the United States by 2050, with almost 1 million people expected to newly develop the disease every year[1]. In 2021, AD represented the seventh in leading causes for all deaths in the U.S., and, while deaths resulting from stroke, HIV, and heart disease all decreased between 2000 and 2021, the number of reported AD deaths increased by more than 140%[2]. Given that AD marks a global health threat and that there have been countless failures in clinical trials to mitigate the disease, it is critical to recognize the complexities of treating AD[3].

Sex differences in AD risk, onset, and progression have become increasingly apparent. AD seems to impact men and women differently, with women having greater lifetime risk for AD than men[4]. AD has additionally shown greater incidence and prevalence in women than men, exemplifying a key sexual dimorphism in AD that has been and must continue to be explored[5–10]. Sex-specific differences in AD could emerge due to a variety of factors, including sex-specific genetic and chromosome effects on disease progression. Sex hormones, such as estrogen, may affect the accumulation of tau as well as that of beta amyloid (Aβ), two major hallmarks of AD, contributing to divergent disease severity and AD progression timelines for men and women. Furthermore, certain symptoms of AD may be associated with a specific sex, while being uncommon for the other.

While AD preclinical studies and clinical trials have historically been largely limited to male populations, recent comparisons of AD onset and progression between sexes affirm the existence of sex-specific variances in AD that are critical to incorporate into clinical practice. Given such biological distinctions, it is imperative to address the sex of a patient in evaluating and treating their AD. Harmful misrepresentations of the general AD population and overgeneralizations drawn from male-dominant data lead to patients being unable to receive the most effective and safe treatments for their circumstances and hinder the entire field from further developments.

Sex-Based Genetic, Chromosomal, Hormonal, and Risk Variance in AD

Sex Differences in Microglial Gene and Function Regulation

In the brain, microglia are key immune cells, activated to react to neuronal damage, infection, and other critical stimuli in order to preserve brain homeostasis. Upon chronic activation, they contribute to the neuroinflammation that is a hallmark of neurodegenerative diseases, becoming hyper-reactive and hypersensitive and releasing molecules associated with neurotoxicity[11]. Ultimately, this inflammatory nature factors into the role microglia are implicated to have in AD pathogenesis.

There are several microglial gene expression differences between female and male AD mice. One study of gene expression, executed with microglia isolated from male and female APP/PS1 mice brains, performed analysis on genotype-related differences, finding that genes characteristic of disease-associated microglia (DAMs) and activated response microglia (ARMs) were upregulated to a greater extent in microglia from female APP/PS1 mice than male APP/PS1 mice. These upregulated genes included genes such as H2-D1, Cd74, Cd9, and Csf1, to name a few, along with Apoe, Trem2, Bin1 and Cd33, which are associated with altered risks of AD. Genes known to become upregulated in inflammatory conditions followed a similar trend: genes like Mertk, Tgfb1, Ccr5, Cybb, and Il1b increased more in aged female mice than in APP male mice, perhaps indicating preparedness. A downregulation of P2ry12, a gene that identifies homeostatic microglia, and an upregulation of genes that typically increase in disease models, such as Fth1 and Lyz2, also

stood out in APP female mice. Additional recorded sex- and genotype- associated changes in protein-encoding genes related to inflammation, oxidative stress, antigen presentation, and microglial motility and were often greater in female APP/PS1 mice as well. Upregulation of Gapdh, Pgk1, and Pgam1, genes coding glycolytic enzymes, was also significantly greater in female APP/PS1 mice. Such upregulation, specifically occurring in females, of genes relating to increased activation of microglia may indicate the microglia of females to be more prepared for change compared to the microglia of males. Potentially, this greater activation could also suggest microglia of females to be more dysfunctional or impaired in their ability to provide neuroprotection, which could be explanatory of AD severity in women [12].

Another study observed sex-related downregulation of the microglial genes that support mitochondrial function and encode mitochondrial enzymes, transporters, and proteins crucial to the architecture of the mitochondrial membrane, suggesting a greater disruption of mitochondrial functions in female microglia that perturbs microglial duties and may contribute to a sex-dependent distinction in risk [13].

These microglial differences are key to understanding the link between sex and immune modulation in AD, particularly as cellular and signaling mechanisms specific to males or females in immune modulation remain unclear. Because the activation of reactive glial cells is involved neuroinflammation, these findings are of significant relevance, but other factors, such as viral infection, obesity, Ca^{2+}/Mg^{2+} dyshomeostasis, may also contribute to inflammation [14].

Sex-Specific Gene Variants and AD Risk

For late-onset AD, the most prominent genetic risk factor is recognized to be the $\varepsilon 4$ allele of the apolipoprotein E (APOE), a main cholesterol transporter assisting lipid transfer and brain injury repair [15]. A study investigating the correlation between APOE alleles, sex, and AD, showed the risk of developing AD that is posed by the apolipoprotein E $\varepsilon 4$ allele to female and male carriers. The study results showed females aged 65-75 years old with the genotype APOE $\varepsilon 3/\varepsilon 4$ had a 1.5-fold greater risk of AD than males in the same age group, while another study found increased AD risk in APOE $\varepsilon 3/\varepsilon 4$ carriers across all ages [16]. For the APOE $\varepsilon 2/\varepsilon 3$ genotype, sex-based effects on AD risk have been unclear, but it is suggested to be more protective for women than for men. The sex-dependent risk may be exacerbated by tau, supported by evidence that $\varepsilon 4$ females with mild cognitive impairment (MCI) have greater tau loads than MCI males. A reasoning for increased AD risk in females with $\varepsilon 4$ alleles has been theorized to be estrogen, which may suppress ketone bodies that the brain relies on as bioenergetic fuel [17]. This theory is supported by evidence that estrogen leads to worse cognitive performance for APOE $\varepsilon 4$ women [18].

Differential Expression of Chromosome-Related Genes

The X and Y chromosomes play critical roles in expressing hundreds of genes. The X chromosome composes 5% of the genome, carrying an immense number of genes expressed in the brain and implicated in several intellectual disabilities. While men have only 1 X chromosome, of the 2 X-chromosomes in each of a woman's cells, 1 experiences random X chromosome inactivation (XCI); however, 30% of X chromosome genes appear to escape XCI. An X-chromosome wide association study performed in AD investigated the genes escaping XCI, finding 4 low-impact X-chromosome loci that seemingly escaped XCI and that exhibited genetic associations between nearby regulation of gene expression and AD risk: NLGN4X, MID1, ZNF280C, and ARGRG4. Particularly, MID1, which demonstrated a significant female association, has been linked to androgen receptor levels, implying a possible influence of hormonal factors. These findings could explain lesser-distinct sex differences, such as increased AD incidence for older women, elevated tau burden in women, or female resilience to AD [19]. Such female resilience was explored through a similarly driven study to uncover the impact of the possession of a second X chromosome on AD risk. For gonadectomized male mice and hAPP female mice, the presence of a second X chromosome was correlated with lower mortality and brain dysfunction. Partially, this durability was endowed by the second X chromosome through KDM6A, a gene escaping XCI and associated with slower cognitive decline. Meanwhile, UTY, the Y paralog of KDM6A, failed to similarly reduce AD-related toxicity [3]. Other factors could affect these X chromosome-linked impacts, such as the difference between female and male mice models in the expression of a few X-linked genes [20].

Sex-Specific Epigenetic Attributes and AD

In addition to chromosomes, epigenetics has also been understood by multiple researchers to contribute to sex-based variances in disease vulnerability and functions of the brain [21–24]. Particularly, DNA methylation profiles notably vary with sex at several loci of adult brains, and several neurological disorders such as AD are tied to adjustments of DNA methylation quantities [25–27]. Sex-specific analysis exposed methylation differences between sexes: a large portion of significant loci, while being still the same direction, showed in the other sex a decreased effect magnitude for the association between methylation and AD Braak stage. Additionally, the analysis found distinct methylation differences unidentified by sex-combined analyses at 84 CpGs and 42 DMRs as they were significant in one sex while not in the other. Most relevantly, a locus at cg22632947 that is mapped to the PRKCA gene, which encodes a protein (kinase Ca) pertinent to the synaptic loss due to the accumulation of $A\beta$ in AD, is highly significant in female samples while not in male samples. On the other hand, methylation-Braak stage

association was highly significant in male samples, while not in female samples, at the locus cg18942110, which is in the promoter of the CRTC3 gene that coactivates the transcription factor CREB. Importantly, CREB plays several roles including maintaining synaptic plasticity, easing short- to long-term memory, and mediating AD-induced synapse loss[28]. Epigenetic aging clocks refer to reliable estimators of biological age based on DNA methylation in CpG islands[29]. Interestingly, in some instances, the slower rates of DNA methylation aging in women explain their superior cognitive performances relative to men; particularly, women's slower GrimAgeAccel rates than men's explained their faster processing speeds. Such findings allow medical assessments to better distinguish cognitive decline driven by disease, such as AD, from natural cognitive decline due to age in a sex-specific manner[30].

Androgens and Other Sex Hormones in AD

Outside of explicit genetics, sex hormones contribute to risk factors for AD. Notably, numerous studies have identified an increased risk of AD after individuals undergo androgen deprivation therapy (ADT), while studies that did not can be attributed to issues with study samples and insufficient clinical variables[31–36]. This elevated risk of AD may be due to the neuroprotective effect of testosterone in AD, as it has been shown to minimize accumulation of Aβ and neuronal death and improve synaptic plasticity[36]. Testosterone, along with estradiol and progesterone (a female sex hormone), has also been found to regulate estrogen receptor 1 (ESR1), which has been implicated in cognitive impairment, thus demonstrating a possible capability of steroid hormones to improve impairment. In addition, these hormones regulated notable miRNAs and transcription factors, such as the NF-κB protein family, that have been implicated in cognitive impairment, revealing anti-inflammatory effects[37].

Alternate Risk Factors in AD

Outside of explicit hormonal differences, sources behind risk factors from AD can also appear from elements such as brain structure and psychosocial stress responses[14]. As such, it becomes critical to evaluate these areas as origins of the dimorphism in AD. Men's typically greater cerebral brain volume may dispose them to greater resistance to AD pathology and brain reserve[38]. In fact, studies have shown less or slower atrophy in males compared to females, reflected also in MCI and AD patients[39–41]. On the other hand, in women, research has found greater, possibly protective cortical thickness, as well as the unique display of dangerous alterations in white matter and mitochondria proteomes[14,42]. These alterations suggest faster neurodegeneration and greater pathology sensitivity in women[14].

Changes in the structure and the function of the brain may also source neuropsychiatric disorders, including post-traumatic stress disorder and depression, and psychosocial stress responses, which can be independent AD risk factors. With depression being a risk factor for AD and being more prevalent in women, it is critical to explore the association between depression and AD for sex-specific connections[14]. While moderate/severe depressive symptoms have been correlated with a twofold increase in risk of MCI in women, several studies have conversely found such a correlation to be unique to men[43]. More research must be done to clarify these inconsistencies.

Like depression, women are also generally more prone to sleep disorders and issues, particularly in menopause, although do men experience sleep apnea at earlier ages. Ultimately, increased problems of sleep in women may convey risk for AD, with Aβ production primarily occurring during hours awake and Aβ clearance occurring in sleep. Similarly, stress has been correlated with AD and cognitive impairment, as corticotrophin releasing factor 1 has been tied to AD. In regards to stress, women also exhibit more vulnerability, and women with mild-to-moderate AD show higher cortisol levels. Thus, stress may also convey increased AD risk for women[14].

Sex-Dependent Pathology in Alzheimer's Disease

Amyloid Beta (Aβ) Accumulation and Plaque Load

As mentioned above, genetics and other risk factors result in AD by manifesting in AD pathology, such as Aβ. Amyloid beta (Figure 1), a proteolytic product common to several neurodegenerative diseases, is a driving force of AD[15]. Aβ, as well as tau, can incite neuroinflammation as well as gliosis, and cyclically, neuroinflammation, characterized by the activation of microglia and astrocytes, results in increases in Aβ accumulation and inflammatory cytokines in AD progression[14]. In particular, astrocytes, the most abundant cell type in the brain, further Aβ load by secreting notable amounts of Aβ; in fact, reactive astrocytes exhibit greater quantities of amyloid precursor protein, γ-secretase, and β-secretase—the three necessary elements for the creation of Aβ[44].

In transgenic mice with mutations in APP and PSEN1, Aβ deposits form in the CNS around 8 to 10 months of age. In studies characterizing these mice, elevated levels of Aβ40 and Aβ42, as well as senile plaque loads, were significantly greater in female mice as compared to male mice aged at 15 months and 19 months. In mice aged 15 months, the area taken by plaques in females represented nearly triple of that in male Tg2576 mice[45]. Similarly, cerebral Aβ was greater in female mice when compared to male mice[46]. In the subiculum of the hippocampal complex of 3xTg-AD mice, comparable findings of greater and faster Aβ accumulation in female mice aged 11-14 months have been established[47–50].

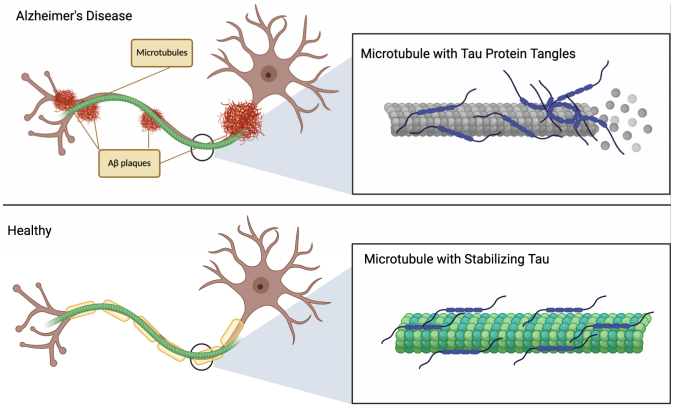

Fig. 1 AD Pathology. Aβ plaques accumulate extracellularly to inhibit proper synaptic connectivity and neuronal signaling in AD patients, while the microtubule-stabilizing tau protein forms tangles.

The sex hormone estrogen has been implicated in the Aβ levels in female APP/PS1 mice, as shown by ovariectomy studies and estradiol replacement[51]. Studies of cell-based and animal models reveal that estrogen seems preventative to AD pathology, proposing that estrogen can lessen Aβ levels by stimulating the production of vesicles with amyloid precursor protein from the trans-Golgi Network[52,53]. In a mitochondrial study of 3xTg AD mice, ovariectomy produced greater accumulation of mitochondrial Aβ, while estrogen treatment reversed these levels. Further research must be done to establish mechanisms of this particular protective effect; however, explanations of this protective role may be that it occurs through transcription of PGC1α, mitofusins, and mtDNA[53]. As mentioned in the previous topic, testosterone has similarly been implicated in Aβ levels as well.

Importantly, these findings in mice models display translational limitations to humans, likely due to an inability of mice models to truly mimic human processes and sex-specific functions, such as menopause, in a fully representative manner. Studies have either established no association or a minimal increase of Aβ burden in human women[54]. However, while sex has not been correlated with global Aβ burden in humans, even in those with APOEε4, sex-specific effects still may occur at earlier ages of menopause for women or Aβ accumulation may occur at a faster rate within women. In fact, for those with parental history of AD, data has indicated that women, as they near the age of their parents' AD symptom onset, usually see Aβ accumulation at a greater pace than men[55]. In individuals with a low CSF Aβ-42 level, being female was additionally associated with greater left hippocampal atrophy and an accelerated decline in memory and performance of executive function[56].

Tau Hyperphosphorylation and Tangle Formation

Tau (Figure 1), another significant factor in the neuropathology of AD, is a phosphoprotein prevalent in axons that, in microtubules, promotes polymerization and stabilization[15]. In a study demonstrating spatial patterns of tau burden as possible biomarkers of AD, women possessed more tau than men in tempero-parietal as well as anterior frontal regions of the brain[57]. Within a sample of clinically normal older adults and AD adults, greater concentrations of plasma p-tau181 in the cerebrospinal fluid (CSF) were found in women as opposed to men, and high quantities of plasma p-tau181 were associated in greater strength with more cortical AB deposition in women than men[58]. In addition, women have been shown to have higher levels of CSF t-tau than men[59]. In clinically normal individuals with high Aβ burden, women demonstrated greater temporal EC tau. Additionally, a stronger association has been established in females between tau retention and APOE ε4, as compared to males[54,59].

Considerable differences between males and females have also been observed by a multi-omics study in effects of 15 metabolites. In fact, while smaller sex-specific associations were discovered between metabolites and CSF Aβ levels, the most notable differences were those in associations between metabolites and CSF p-tau levels: higher CSF p-tau was associated with greater levels of medium-chain acylcarnitine C10 in specifically females. Considering that late-onset AD is partially considered a metabolic disorder, the study's findings are particularly remarkable, implying that women, as compared to men, encounter more impairment of mitochondrial energy production[60].

Menopause has been implicated in the sex-based differences of tau burden. In post-menopausal women, significantly greater tau-PET signal has been observed in parieto-occipital regions as compared to men of the same age group. Meanwhile, no such difference was observed between women that were pre-menopausal and men. In the rostral middle frontal and the inferior parietal and lateral occipital regions, the status of menopause moderated association between sex and tau-PET signal. These findings suggest an interval of tau vulnerability in women at the time of menopause that may be independent of APOEε4 and Aβ burden[61].

Sex-based differences in autophagy, which is a process that enables the clearance of Aβ and tau aggregates and that is majorly regulated by sex hormones including androgen and estrogen, have additionally been associated with the increased tau aggregation in females. Women, who throughout their lifetimes have lower basal autophagy than men, may have greater vulnerability to AD due to this decreased ability to clear aggregates that could result in continually sustaining pathology[53].

In addition, quantities of regional neurofibrillary tangles have been found to differ between men and women. While the number of neurofibrillary tangles in the neocortex of men has been demonstrated to undergo a more than twofold decline in the 8th decade, women experience a twofold decreased severity later in their 9th century. Although men experienced a similar decrease

in severity of hippocampal neurofibrillary tangles, women contrastingly were observed to have increased neurofibrillary tangle amounts in hippocampal regions with age[62]. Interestingly, X-Chromosome gene expression has been associated with NFT burden in men, while it has not been in women[63].

Iron Accumulation and Cellular Senescence

Alongside the implication of amyloid and tau in AD pathogenesis, iron accumulation has increasingly been recognized to affect neurodegeneration, demonstrating key patterns in AD independent of amyloid and tau[64]. Sex-dependent iron accumulation has also been identified with AD, as significantly more iron+Iba1+ cells have been demonstrated in the tissue of female AD patients when compared to that of male AD patients, a result consistent in female and male APP/PS1 mice. Iron accumulation has specifically been linked to dystrophic microglia, which are microglia demonstrating spheroids, removed branches, beaded processes, and rod-shaped cell bodies, as well as glycolysis. These links further signal that iron drives increased neuroinflammation in AD; for instance, the accumulation of iron triggers microglial production of inflammatory cytokines[13,65]. This indicates a greater burden of neuroinflammation in females.

Cellular senescence, a cell cycle arrest in aged and damaged cells, can lead to chronic inflammation and the dysfunction of tissue, and senescent cells have been shown to promote the development of AD (Figure 2). Particularly, the accumulation of p16 has been demonstrated to be characteristic of late senescence. Cells undergoing senescence additionally amass lipofuscin, which is a substance that holds lipids and is created through lysosomal digestion[66]. Lipofuscin and p16, similar to iron, also point to dystrophic microglia. For both female mice as well as female AD patients, they have been reported to experience greater accumulation of both p16 and lipofuscin when compared to their male counterparts, specifically demonstrated in the microglia of female mice. These results have indicated greater amounts of cellular senescence in the tissue, particularly in the microglia, of female AD patients compared to male patients, contributing to a notion of increased damaging and self-reinforcing neuroinflammation in women[13].

Vasculature in AD Pathology

In addition to the aforementioned burdens in the progression of AD, cardiovascular risk factors contribute critically to the pathogenesis of AD, with a majority of vascular cognitive impairment (VCI) patients developing dementia[68]. These factors, such as diabetes, obesity, atherosclerosis, and hypertension, result in weakened clearance of Aβ, greater oxidative stress, hypoxia, decreased cerebral blood flow, and interference to the blood brain barrier, all eventually leading to dementia with a possible cyclical effect[14].

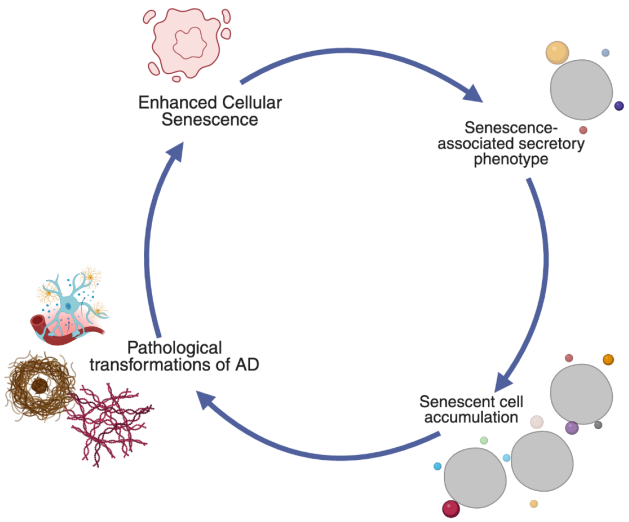

Fig. 2 The cycle of cellular senescence in AD. Pathological changes in AD reinforce cellular senescence. This senescence incites senescence-associated secretory phenotype (SASP), which decreases the clearance of senescent cells in AD, leading to accumulation of these cells. This accumulation then further perpetuates the pathology of AD, reinforcing the cycle[67].

Interestingly, the incidence of coronary artery disease, a vascular risk factor tied to cognitive decline through brain microvascular lesions, is much greater in men than women across all age categories. This too may be due to the protective nature of estrogen in females against atherosclerosis, oxidative stress, and inflammation. Meanwhile, other vascular risk factors are unique to women, specifically hypertensive pregnancy disorders that are associated with cognitive impairment and brain lesions[14]. In fact, in women around the age of 60, brain atrophies, as well as lower processing speeds, have occurred more in those with a history of hypertensive pregnancy disorders compared with those without[69]. Differences between sexes have also been reported in cerebral small vessel diseases, which lead to inhibited perfusion of brain regions and, as such, are suggested to play a role in AD[14]. In these diseases, an association has been proposed between the female sex and disease progress, and, in only women, apolipoprotein A-I and high-density lipoprotein cholesterol were negatively associated with white matter lesion severity[14,70]. Thus, sex differences in vasculature are inextricably linked to a complete assessment of the sex-specific nature of AD, and this, as well as all sex-dependent pathological progressions in AD, is a critical understanding necessary to evaluate symptoms.

Transcriptional Response to AD Pathology

Single-cell transcriptomic analysis of AD additionally found sex-specific differential responses including several cell-types.

Most significant were in oligodendrocyte and neuronal cells. In males, greater pathology was uniquely associated with a global transcriptional activation in oligodendrocytes, while increased pathology in females was associated with a global downregulation of gene activity in inhibitory neuronal cells as well as excitatory neuronal cells. These responses in female neuronal cells were much more pronounced than those in males, with male inhibitory neurons exhibiting no clear shift in response to pathology (besides slightly to amyloid) and male excitatory neurons displaying lesser responses. Furthermore, the observed reduced female transcriptional response in oligodendrocytes is accordant with findings that white matter lesion volume solely correlates with lower cognition in females. Ultimately, while stating the need for further explanation, the analysis suggests these findings may imply either a larger burden of transcriptional disease or more disease resilience in females[71].

Sex-Dependent Symptoms of AD

Cognitive Symptoms

The neuronal dysfunction caused by AD pathology manifests into cognitive, neuropsychological, and behavioral symptoms in AD that may occur on a sex-specific basis. Several differences in cognitive symptoms have been observed between female and male AD patients. In AD, notable symptoms include a decline in verbal and semantic capabilities. Multiple investigations have found that women AD patients, when compared to men with comparable AD severity, suffered intensified disablement of their semantic memory, exemplified particularly through their performance in confrontation naming task[72,73].

Visuospatial abilities include those involving spatial perception and memory, navigation abilities, and an individual's capabilities to rotate objects in their mind. Deficits in visuospatial capacities are prevalent in AD patients, hindering their achievement of several tasks[72]. Interestingly, after the onset of amyloid, men have revealed steeper rates of cognitive decline as compared to women, specifically in visuospatial and executive capabilities[74]. Similar to semantic memory, an advantage in visuospatial episodic memory has been observed in male AD patients compared to female; this is a sexual dimorphism unseen in mild cognitive impairment (MCI) patients[75]. In tasks that necessitated the active manipulation of visuospatial intake, AD men exhibited greater performance than women as well[76]. However, several studies contradictingly show no significant differences between male and female AD patients in their visuospatial abilities. Yet, these results still possibly illustrate sex-specific effects on visuospatial abilities. Across typical elderly populations absent of AD, males have been established to have a visuospatial advantage, one which we may expect to persevere in AD patients; therefore, sex-specific effects of AD could actually be responsible for equalizing their performance[72].

This sexual dimorphism in cognitive symptoms could be attributed to various sex-specific factors, including hormonal impacts on decline through female estrogen loss or an increased male cognitive reserve. Here it is also noteworthy that sex distinctions exist within the neuro-immune modulation of cognitive performance and memory, such as cytokine activation, that may be relevant to this dimorphism[77]. Ultimately, findings indicate a more severe and widespread deterioration of cognitive function of females with AD[72].

Neuropsychiatric and Behavioral Symptoms

In AD patients, neuropsychiatric symptoms (NPS) are also very prevalent, yet there exists considerable clinical variability in the onset of these symptoms in AD patients. NPS have been connected to multiple harms and negative impacts for AD patients, including greater mortality, more severity in cognitive decline, as well as burden on caregivers[78]. Given the significance of NPS, it is important to recognize the variances in NPS that exist between females and males.

In a meta-analysis of sex differences in NPS within AD patients, the female sex was linked to a greater prevalence of psychotic symptoms, depressive symptoms, the onset of delusions, as well as aberrant motor behavior than males with AD[79]. It has also been demonstrated that a greater number of women with AD had a combination of such symptoms as compared to men with AD. In women, agitation has been linked to a majority of psychiatric issues, while, in males, it has solely been linked to paranoia[80]. Women were also demonstrated to be slightly more prone to verbal and physical aggression as well as irritability and reclusivity[81].

Meanwhile, male AD patients have shown increased severity in apathy compared to females with AD[79]. Additionally, men with AD have exhibited increased behaviors demonstrative of vegetative changes, including excess of sleeping and eating[81]. Interestingly, in elderly individuals with probable AD, there has also been a sex-based association found between depressed moods and dependence, with depressed moods only predicting an accelerated exacerbation of dependence on others in men rather than women[82].

While these sex-based differences in NPS could be due to the effects of sex hormones, such as those of estradiol on increased risks of depression and AD, further research could provide other possible explanations[79,82].

Discussion

The extent of sex differences in AD makes it essential to take sex into consideration when treating AD. This imperative becomes apparent when evaluating clinical trials, as recognition of sex in the trial stages of drugs ensures that results are not harmfully

represented as true for all. Here, it becomes particularly essential to recognize an inevitable disconnect between animal studies and human studies, or that between preclinical studies and clinical studies, in evaluating behavior and cognitive performance, disease course, and prognosis in AD. Mouse models particularly fail to demonstrate realistic effects of human menopause and estrogen in AD, which is an issue exacerbated by AD's uniqueness in humanity [14]. Even if mouse studies improve in female representation, establishing clinical trials that are representative of both sexes avoids translational issues to a true clinical setting. As a result, AD patients can receive the best and optimal care for their unique circumstances. Several drugs and treatments perform differently for males as compared to females, creating unbalanced effects on AD women as compared to AD men that could be due to many factors. As previously stated in the review, the outcomes of a treatment could be affected by sex hormones, including estrogen and its impact on the mechanistic level in AD, and the impacts of menopause. Other influences on outcomes could include genetic differences, as perpetuated by XCI, or the variance in pathological accumulation of tau, neurofibrillary tangles, and Aβ between females and males. With this contradictory progression of AD, the manifestation of symptoms also differs between men and women, which can lead to contrasting symptomatic effects when treatment is attempted.

Lecanemab, an FDA-approved amyloid antibody drug that is meant to decrease cognitive and functional decline in AD patients, has been shown to be more effective in its treatment for men rather than women [83]. While current research does not have the capacity to explain this difference, the dimorphic drug response may be due to a difference in amyloid clearance, for example, which is linked to lecanemab's mechanism of action [84]. Similarly, davunetide, which is a tauopathy and neurodegeneration inhibitor acting as replacement therapy when activity-dependent neuroprotective protein (ADNP) is deficient, also demonstrates sexual dimorphism. In a clinical trial of davunetide, dose-dependent cognitive function improvements were significantly observed in a test of visual matching in men rather than women. Women, however, in a test of working semantic memory and attention, significantly exhibited high-dose improvement with davunetide. The sex-based dimorphism here may be linked to estrous cycle's modulation of ADNP or ADNP's greater expression in female hippocampi [85]. Another clinical trial demonstrated that sodium benzonate, which offsets oxidative stress and aids in neuroprotection, results in greater catalase for women, while it does not for men, especially in 1000 mg doses. These increases in catalase were associated with greater cognitive improvement in these women. On a mechanistic level, such differences may originate from the sex-specific neurodegeneration and cognitive modulation contrasts in oxidative stress and NMDA receptor dysfunction, like testosterone's role in oxidative stress [86]. In AD, another drug sildenafil has been associated with decreased incidence of AD. While a clinical trial has yet to be performed with sildenafil, a recent study found that sildenafil usage was associated with a greater decreased risk of AD for males than women, although these findings might be attributed to the fact that the data collected for the study was skewed male-dominant. However, these results also may be because of sexual dimorphism in AD biomarkers, as sildenafil has a relationship with genes that are associated with tau tangles and amyloid [87]. In a recent EMERGE trial as well, cognitive benefits of the intervention were specific to men [88]. Unfortunately, because stratification by sex is currently left unconsidered by large, there is a scarcity in publications that show clinical and biomarker data of sex differences in AD trials, as well as the mechanisms behind those differences. However, such reports of varying outcomes in trials and studies on the basis of sex contribute to evidence that the efficacy of drugs is largely impacted by the sex of the patient [89].

It is crucial to note here that the observed sex-specific differences in AD discussed in this review may also differ across variations in other factors influential to AD, including brain structure, ethnicity, age, education, and socioeconomic status. Additionally, sex-specific differences may vary across AD subtypes. For example, African-American females have been specifically associated with late-onset AD, though this may be due to larger clinical manifestations in society [90]. Although a large portion of studies mention only late-onset AD, sex differences also appear in early-onset AD. In early-onset AD, women demonstrated greater atrophy burden and cognitive impairment than men in comparison to healthy controls of the same sex, and women with early-onset AD had higher CSF tau levels men, mirroring findings in the general AD population [91]. However, this existing research on sex differences in early-onset AD pathology should be expanded upon. Stages of AD should also be considered, as women's greater average lifespan may contribute to sexually dimorphic general AD statistics [14]. For example, women may demonstrate early disease resistance to AD, with an early defense to metabolic dysfunction; additionally, women at reproductive ages produce lower quantities of hydrogen peroxide, homocysteine, and NADPH oxidase and greater quantities of antioxidant enzymes than men [53]. In fact, women with mild-to-moderate AD, before adjusting for brain metabolism, showed cognitive advantages compared to men [92]. Importantly here, when evaluating such sex differences in AD across age groups, the decrease in estrogen levels that arrives with menopause also becomes crucial to consider [53].

Historically, females have been underrepresented or completely excluded from clinical trials and research. As a result, the scientific standard has been set by male in vitro and in vivo models, catering to and disproportionately benefitting the male population. In the modern-day, steps have been taken to limit such undercoverage by studies, including requirements by publication guidelines and by government funding bodies to include balanced representation in studies and sex-based analyses. This

commitment to improve is exemplified by the Sex and Gender Equity in Research Policy and the National Institutes of Health[89].

However, while recent studies have improved in including a balanced number of men and women, they continue to disregard noteworthy findings of sex-based dissimilarities in effects. As demonstrated by aforementioned trials, several drugs operate on a sex-specific basis in mitigating AD; thus, it is likely that many others have similar limitations that remain alarmingly unexplored and unnoticed. In fact, a study reported that out of 118 identified dementia trials, only 8 described sexual dimorphism in outcomes. A failure to specify mitigatory benefits in AD progression to the sex that they are evident in could lead to exacerbated differences between the health of men and women when prescribed the same drug. Such gaps manifest into structural inequities in healthcare, which becomes particularly harmful for the wellbeing of patients and inhibits further developments in the field. In clinical practice, this could create the illusion of prescribing the best treatments for AD symptoms, when, in reality, they could be ineffective for those of a particular sex, and those patients are left largely untreated[89]. This is particularly dangerous in AD, with its nature as a progressive and time-sensitive disorder in which symptoms worsen. Furthermore, the excessive AD load on females and the clear, vast distinctions in AD mechanisms and progression between men and women, as demonstrated by this review, exhibit the need to recognize sex-dependent risk factors and therapeutic effects.

As we progress in our acknowledgement of sexual dimorphism in clinical trials going forward, it becomes possible to expand knowledge that is particular to the impacts of certain drugs. With specificity in trials, we can begin to establish with confidence reasons for why a certain drug's behavior is reliant on sex as well as specific connections to one of many possible factors in the timeline of the disease. In turn, we must use our mechanistic understanding to create treatments tailored to each sex. Ultimately, this will allow the field to target progression in men and women more effectively and to improve current drugs, expanding the scope of treatments and healing current inequalities in healthcare.

Methods

For this paper, I used PubMed as a search engine to look through relevant publications to my topic, with no custom filters. To find papers relating to my subtopics, I initially used the keywords "sex and Alzheimer's Disease" to search for papers sorted by "most recent," choosing those with findings most pertinent to my subtopics and disregarding irrelevant papers. After doing so, I parsed through the references I had already cited for more articles to review, again screening for relevance to my subject. When searching for more papers for a particular subtopic, I searched the subtopic along with "and sex in Alzheimer's," again with results only sorted by "most recent." Regarding my exclusion criteria, I attempted to primarily review peer-reviewed publications from the past 15 years; however, when I did cite papers published before that point, I made sure that the findings I cited are still consistent with modern-day research and are still actively being cited within the field. When confronted with conflicting findings, I mentioned them in this review and suggested explanations as to why they may contradict other studies.

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References

1 *Alzheimer's disease facts and figures (2016), Alzheimer's & Dementia 459-509*.

2 *Alzheimer's disease facts and figures (2024), Alzheimer's & Dementia, 3708-3821*.

3 E. Davis, L. Broestl, S. Abdulai-Saiku, K. Worden, L. Bonham, E. Miones-Moyano, A. Moreno, D. Wang, K. Chang, G. Williams, B. Garay, I. Lobach, N. Devidze, D. Kim, C. Anderson-Bergman, G.-Q. Yu, C. White, J. Harris, B. Miller, D. Bennett, A. Arnold, P. Jager, J. Palop, B. Panning, J. Yokoyama, L. Mucke and D. Dubal, *A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease*.

4 *Alzheimer's disease facts and figures (2021), Alzheimer's & Dementia, 327406*.

5 D. Bachman, P. Wolf, R. Linn, J. Knoefel, J. CobbS, A. Belanger, R. D'Agostino and L. White, *Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study*.

6 A. Ruitenberg, A. Ott, J. Swieten, A. Hofman and M. Breteler, *Incidence of dementia: does gender make a difference?*

7 A. Jorm and D. Jolley, *The incidence of dementia*.

8 A. Jorm, A. Korten and A. Henderson, *The prevalence of dementia: A quantitative integration of the literature*.

9 W. Rocca, L. Amaducci and B. Schoenberg, *Epidemiology of clinically diagnosed Alzheimer's disease*.

10 K. Andersen, L. Launer, M. Dewey, L. Letenneur, A. Ott, J. Copeland, J.-F. Dartigues, P. KraghSorensen, M. Baldereschi, C. Brayne, A. Lobo, J. MartinezLage, T. Stijnen and A. Hofman, *Gender differences in the incidence of AD and vascular dementia*.

11 I. Holtman, D. Raj, J. Miller, W. Schaafsma, Z. Yin, N. Brouwer, P. Wes, T. Mller, M. Orre, W. Kamphuis, E. Hol, E. Boddeke and B. Eggen, *Induction of a common microglia gene expression signature by aging and neurodegenerative conditions: a co-expression meta-analysis*.

12 M.-V. Guillot-Sestier, A. Araiz, V. Mela, A. Gaban, E. O'Neill, L. Joshi, E. Chouchani, E. Mills and M. Lynch, *Microglial metabolism is a pivotal factor in sexual dimorphism in Alzheimer's disease*.

13 E. O'Neill, V. Mela, A. Gaban, S. Bechet, A. McGrath, A. Walsh, A. McIntosh and M. Lynch, *Sex-Related Microglial Perturbation Is Related to Mitochondrial Changes in a Model of Alzheimer's Disease*.

14 D. Zhu, A. Montagne and Z. Zhao, *Alzheimer's pathogenic mechanisms and underlying sex difference*.

15 B. Dugger and D. Dickson, *Pathology of Neurodegenerative Diseases*.

16 S. Neu, J. Pa, W. Kukull, D. Beekly, A. Kuzma, P. Gangadharan, L.-S. Wang, K. Romero, S. Arneric, A. Redolfi, D. Orlandi, G. Frisoni, R. Au, S. Devine, S. Auerbach, A. Espinosa, M. Boada, A. Ruiz, S. Johnson, R. Koscik, J.-J. Wang, W.-C. Hsu, Y.-L. Chen and A. Toga.

17 B. Riedel, P. Thompson, R. Brinton and Age, *APOE and sex: Triad of risk of Alzheimer's disease*.

18 K. Yaffe, M. Haan, A. Byers, C. Tangen and L. Kuller, *Estrogen use, APOE, and cognitive decline*.

19 M. Belloy, Y. Guen, I. Stewart, K. Williams, J. Herz, R. Sherva, R. Zhang, V. Merritt, M. Panizzon, R. Hauger, J. Gaziano, M. Logue, V. Napolioni and M. Greicius, *Role of the X Chromosome in Alzheimer Disease Genetics*.

20 D. Skuse, *X-linked genes and mental functioning*.

21 G. Dunn, C. Morgan and T. Bale, *Sex-specificity in transgenerational epigenetic programming*.

22 Y. Menger, M. Bettscheider, C. Murgatroyd and D. Spengler, *Sex Differences in Brain Epigenetics*.

23 M. McCarthy and B. Nugent, *At the frontier of epigenetics of brain sex differences*.

24 K. Burghardt, J. Pilsner, M. Bly and V. Ellingrod, *DNA Methylation in Schizophrenia Subjects: Gender and MTHFR 677C/T Genotype Differences*.

25 H. Xu, F. Wang, Y. Liu, Y. Yu, J. Gelernter and H. Zhang, *Sex-biased methylome and transcriptome in human prefrontal cortex*.

26 P. Jager, G. Srivastava, K. Lunnon, J. Burgess, L. Schalkwyk, L. Yu, M. Eaton, B. Keenan, J. Ernst, C. McCabe, A. Tang, T. Raj, J. Replogle, W. Brodeur, S. Gabriel, H. Chai, C. Younkin, S. Younkin, F. Zou, M. Szyf, C. Epstein, J. Schneider, B. Bernstein, A. Meissner, N. Ertekin-Taner, L. Chibnik, M. Kellis, J. Mill and D. Bennett, *Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci*.

27 K. Lunnon, R. Smith, E. Hannon, P. Jager, G. Srivastava, M. Volta, C. Troakes, S. Al-Sarraj, J. Burrage, R. Macdonald, D. Condliffe, L. Harries, P. Katsel, V. Haroutunian, Z. Kaminsky, C. Joachim, J. Powell, S. Lovestone, D. Bennett, L. Schalkwyk and J. Mill, *Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease*.

28 L. Zhang, J. Young, L. Gomez, T. Silva, M. Schmidt, J. Cai, X. Chen, E. Martin and L. Wang, *Sex-specific DNA methylation differences in Alzheimer's disease pathology*.

29 D. O'Shea and J. Galvin, *Female APOE 4 Carriers with Slow Rates of Biological Aging Have Better Memory Performances Compared to Female 4 Carriers with Accelerated Aging*.

30 D. O'Shea, T. Maynard and G. Tremont, *DNA Methylation GrimAge Acceleration Mediates Sex/Gender Differences in Verbal Memory and Processing Speed: Findings From the Health and Retirement Study*.

31 S. Chung, H. Lin, M. Tsai, L. Kao, C. Huang and K. Chen, *Androgen deprivation therapy did not increase the risk of Alzheimer's and Parkinson's disease in patients with prostate cancer*.

32 J.-H. Hong, C.-Y. Huang, C.-H. Chang, C.-H. Muo, F.-S. Jaw, Y.-C. Lu and C.-J. Chung, *Different androgen deprivation therapies might have a differential impact on cognition - An analysis from a population-based study using time-dependent exposure model*.

33 B. Tae, B. Jeon, S. Shin, H. Choi, J. Bae and J. Park, *Correlation of Androgen Deprivation Therapy with Cognitive Dysfunction in Patients with Prostate Cancer: A Nationwide Population-Based Study Using the National Health Insurance Service Database*.

34 A. Krasnova, M. Epstein, M. Marchese, B. Dickerman, A. Cole, S. Lipsitz, P. Nguyen, A. Kibel, T. Choueiri, S. Basaria, L. Mucci, M. Sun and Q.-D. Trinh, *Risk of dementia following androgen deprivation therapy for treatment of prostate cancer*.

35 H. Ng, B. Koczwara, D. Roder and A. Vitry, *Development of comorbidities in men with prostate cancer treated with androgen deprivation therapy: an Australian population-based cohort study*.

36 H.-L. Jeon, E. Choo, S.-H. Jeong, J. Yun, C. Jeong and H. Lee, *Risk of Alzheimer's disease and Parkinson's disease following androgen deprivation therapy in a real world nationwide cohort*.

37 H. Nguyen, G. Vu and W.-K. Kim, *The molecular mechanisms of steroid hormone effects on cognitive function*.

38 M. Mielke, P. Vemuri and W. Rocca, *Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences*.

39 X. Hua, D. Hibar, S. Lee, A. Toga, C. Jack, M. Weiner and P. M, *Thompson and Alzheimer's Disease Neuroimaging Initiative, Sex and age differences in atrophic rates: an ADNI study with n=1368 MRI scans*.

40 B. Ardekani, A. Convit and A. Bachman, *Analysis of the MIRIAD Data Shows Sex Differences in Hippocampal Atrophy Progression*.

41 M. Elbejjani, R. Fuhrer, M. Abrahamowicz, B. Mazoyer, F. Crivello, C. Tzourio and C. Dufouil, *Depression, depressive symptoms, and rate of hippocampal atrophy in a longitudinal cohort of older men and women*.

42 X. Gallart-Palau, B. Lee, S. Adav, J. Qian, A. Serra, J. Park, M. Lai, C. Chen, R. Kalaria and S. Sze, *Gender differences in white matter pathology and mitochondrial dysfunction in Alzheimer's disease with cerebrovascular disease*.

43 R. Nebel, N. Aggarwal, L. Barnes, A. Gallagher, J. Goldstein, K. Kantarci, M. Mallampalli, E. Mormino, L. Scott, W. Yu, P. Maki and M. Mielke, *Understanding the impact of sex and gender in Alzheimer's disease: A call to action*.

44 G. Frost and Y.-M. Li, *The role of astrocytes in amyloid production and Alzheimer's disease*.

45 M. Callahan, W. Lipinski, F. Bian, R. Durham, A. Pack and L. Walker, *Augmented Senile Plaque Load in Aged Female -Amyloid Precursor Protein-Transgenic Mice*.

46 D. Howlett, J. Richardson, A. Austin, A. Parsons, S. Bate, D. Davies and M. Gonzalez, *Cognitive correlates of A deposition in male and female mice bearing amyloid precursor protein and presenilin-1 mutant transgenes*.

47 Y.-T. Hu, X.-L. Chen, Y.-N. Zhang, H. McGurran, J. Stormmesand, N. Breeuwsma, A. Sluiter, J. Zhao, D. Swaab and A.-M. Bao, *Sex differences in hippocampal -amyloid accumulation in the triple-transgenic mouse model of Alzheimer's disease and the potential role of local estrogens*.

48 C. Hirata-Fukae, H.-F. Li, H.-S. Hoe, A. Gray, S. Minami, K. Hamada, T. Niikura, F. Hua, H. Tsukagoshi-Nagai, Y. Horikoshi-Sakuraba, M. Mughal, G. Rebeck, F. LaFerla, M. Mattson, N. Iwata, T. Saido, W. Klein, K. Duff, P. Aisen and Y. Matsuoka, *Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model*.

49 J. Carroll, E. Rosario, S. Kreimer, A. Villamagna, E. Gentzschein, F. Stanczyk and C. Pike, *Sex differences in -amyloid accumulation in 3xTg-AD mice: Role of neonatal sex steroid hormone exposure*.

50 R. Belfiore, A. Rodin, E. Ferreira, R. Velazquez, C. Branca, A. Caccamo and S. Oddo, *Temporal and regional progression of Alzheimer's diseaselike pathology in 3xTgAD mice*.

51 H. Zheng, H. Xu, S. Uljon, R. Gross, K. Hardy, J. Gaynor, J. Lafrancois, J. Simpkins, L. Refolo, S. Petanceska, R. Wang and K. Duff, *Modulation of A peptides by estrogen in mouse models*.

52 J. Greenfield, L. Leung, D. Cai, K. Kaasik, R. Gross, E. Rodriguez-Boulan, P. Greengard and H. Xu, *Estrogen lowers Alzheimer beta-amyloid generation by stimulating trans-Golgi network vesicle biogenesis*.

53 C. Lopez-Lee, E. Torres, G. Carling and L. Gan, *Mechanisms of sex differences in Alzheimer's disease*.

54 R. Buckley, E. Mormino, R. Amariglio, M. Properzi, J. Rabin, Y. Lim, K. Papp, H. Jacobs, S. Burnham, B. Hanseeuw, V. Dor, A. Dobson, C. Masters, M. Waller, C. Rowe, P. Maruff, M. Donohue, D. Rentz, D. Kirn, T. Hedden, J. Chhatwal, A. Schultz, K. Johnson, V. Villemagne and R. Sperling, *Sex, amyloid, and APOE 4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three wellcharacterized cohorts*.

55 S. Villeneuve, J. Vogel, J. Gonneaud, A. Binette, P. Rosa-Neto, S. Gauthier, R. Bateman, A. Fagan, J. Morris, T. Benzinger, S. Johnson, J. Breitner and J. Poirier, *Proximity to Parental Symptom Onset and Amyloid- Burden in Sporadic Alzheimer Disease*.

56 M. Koran, M. Wagener and T. Hohman, *Sex differences in the association between AD biomarkers and cognitive decline*.

57 J. Pereira, T. Harrison, R. Joie, S. Baker and W. Jagust, *Spatial patterns of tau deposition are associated with amyloid, ApoE, sex, and cognitive decline in older adults*.

58 A. Tsiknia, S. Edland, E. Sundermann, E. Reas, J. Brewer, D. Galasko and S. Banks, *Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression*.

59 T. Hohman, L. Dumitrescu, L. Barnes, M. Thambisetty, G. Beecham, B. Kunkle, K. Gifford, W. Bush, L. Chibnik, S. Mukherjee, P. Jager, W. Kukull, P. Crane, S. Resnick, C. Keene, T. Montine, G. Schellenberg, J. Haines, H. Zetterberg, K. Blennow, E. Larson, S. Johnson, M. Albert, D. Bennett, J. Schneider and A. Jefferson, *Sex-Specific Association of Apolipoprotein E With Cerebrospinal Fluid Levels of Tau*.

60 M. Arnold, K. Nho, A. Kueider-Paisley, T. Massaro, K. Huynh, B. Brauner, S. MahmoudianDehkordi, G. Louie, M. Moseley, J. Thompson, L. John-Williams, J. Tenenbaum, C. Blach, R. Chang, R. Brinton, R. Baillie, X. Han, J. Trojanowski, L. Shaw, R. Martins, M. Weiner, E. Trushina, J. Toledo, P. Meikle, D. Bennett, J. Krumsiek, P. Doraiswamy, A. Saykin, R. Kaddurah-Daouk and G. Kastenmller, *Sex and APOE 4 genotype modify the Alzheimer's disease serum metabolome*.

61 R. Buckley, A. O'Donnell, E. McGrath, H. Jacobs, C. Lois, C. Satizabal, S. Ghosh, Z. Rubinstein, J. Murabito, R. Sperling, K. Johnson, S. Seshadri and A. Beiser, *Menopause Status Moderates Sex Differences in Tau Burden: A Framingham ¡scp¿PET¡/scp¿ Study*.

62 A. Liesinger, N. Graff-Radford, R. Duara, R. Carter, F. Al-Shaikh, S. Koga, K. Hinkle, S. DiLello, M. Johnson, A. Aziz, N. Ertekin-Taner, O. Ross, D. Dickson and M. Murray, *Sex and age interact to determine clinicopathologic differences in Alzheimer's disease*.

63 E. Davis, C. Solsberg, C. White, E. Miones-Moyano, M. Sirota, L. Chibnik, D. Bennett, P. Jager, J. Yokoyama and D. Dubal, *Sex-Specific Association of the X Chromosome With Cognitive Change and Tau Pathology in Aging and Alzheimer Disease*.

64 M. Bulk, W. Abdelmoula, R. Nabuurs, L. Graaf, C. Mulders, A. Mulder, C. Jost, A. Koster, M. Buchem, R. Natt, J. Dijkstra and L. Weerd, *Post-mortem MRI and histology demonstrate differential iron accumulation and cortical myelin organization in early- and late-onset Alzheimer's disease*.

65 R. Holland, A. McIntosh, O. Finucane, V. Mela, A. Rubio-Araiz, G. Timmons, S. McCarthy, Y. Gun'ko and M. Lynch, *Inflammatory microglia are glycolytic and iron retentive and typify the microglia in APP/PS1 mice*.

66 J. Beck, I. Horikawa and C. Harris, *Cellular Senescence: Mechanisms, Morphology, and Mouse Models*.

67 J. Zhu, C. Wu and L. Yang, *Cellular senescence in Alzheimer's disease: from physiology to pathology*.

68 C. Iadecola, M. Duering, V. Hachinski, A. Joutel, S. Pendlebury, J. Schneider and M. Dichgans, *Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel*.

69 M. Mielke, N. Milic, T. Weissgerber, W. White, K. Kantarci, T. Mosley, B. Windham, B. Simpson, S. Turner and V. Garovic, *Impaired Cognition and Brain Atrophy Decades After Hypertensive Pregnancy Disorders*.

70 Z.-G. Yin, Q.-S. Wang, K. Yu, W.-W. Wang, H. Lin and Z.-H. Yang, *Sex differences in associations between blood lipids and cerebral small vessel disease*.

71 H. Mathys, J. Davila-Velderrain, Z. Peng, F. Gao, S. Mohammadi, J. Young, M. Menon, L. He, F. Abdurrob, X. Jiang, A. Martorell, R. Ransohoff, B. Hafler, D. Bennett, M. Kellis and L.-H. Tsai, *Single-cell transcriptomic analysis of Alzheimer's disease*.

72 K. Laws, K. Irvine and T. Gale, *Sex differences in cognitive impairment in Alzheimer's disease*.

73 J. Ryan, L. Umfleet, D. Kreiner, A. Fuller and A. Paolo, *Neuropsychological differences between men and women with Alzheimer's disease*.

74 C. Joynes, M. Bilgel, Y. An, A. Moghekar, N. Ashton, P. Kac, T. Karikari, K. Blennow, H. Zetterberg, M. Thambisetty, L. Ferrucci, S. Resnick and K. Walker, *Sex differences in the trajectories of plasma biomarkers, brain atrophy, and cognitive decline relative to amyloid onset*.

75 U. Beinhoff, H. Tumani, J. Brettschneider, D. Bittner and M. Riepe, *Gender-specificities in Alzheimer's disease and mild cognitive impairment*.

76 X. Millet, N. Raoux, N. Carret, J. Bouisson, J.-F. Dartigues and H. Amieva, *Gender-related Differences in Visuospatial Memory Persist in Alzheimer's Disease*.

77 N. Tronson and K. Collette, *Putative) sex differences in neuroimmune modulation of memory*.

78 H. Wang, A. Chinna-Meyyappan, O. Feldman and K. Lanctt, *Emerging therapies for treatment of agitation, psychosis, or apathy in Alzheimer's disease*.

79 W. Eikelboom, M. Pan, R. Ossenkoppele, M. Coesmans, J. Gatchel, Z. Ismail, K. Lanctt, C. Fischer, M. Mortby, E. Berg and J. Papma, *Sex differences in neuropsychiatric symptoms in Alzheimer's disease dementia: a meta-analysis*.

80 D. Cohen, C. Eisdorfer, P. Gorelick, D. Luchins, S. Freeh, T. Semla, G. Paveza, H. Shaw and J. Ashford, *Sex Differences in the Psychiatric Manifestations of Alzheimer's Disease*.

81 Y. Tao, M. Peters, L. Drye, D. Devanand, J. Mintzer, B. Pollock, A. Porsteinsson, P. Rosenberg, L. Schneider, D. Shade, D. Weintraub, J. Yesavage, C. Lyketsos and C. Munro, *Sex Differences in the Neuropsychiatric Symptoms of Patients With Alzheimer's Disease*.

82 A. Kociolek, K. Fernandez, M. Hernandez, Z. Jin, S. Cosentino, C. Zhu, Y. Gu, D. Devanand and Y. Stern, *Neuropsychiatric Symptoms and Trajectories of Dependence and Cognition in a Sample of Community-dwelling Older Adults with Dementia*.

83 C. Dyck, C. Swanson, P. Aisen, R. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L. Kramer and T. Iwatsubo, *Lecanemab in Early Alzheimer's Disease*.

84 D. Andrews, S. Ducharme, H. Chertkow, M. Sormani and D. L, *Collins and Alzheimer's Disease Neuroimaging Initiative, The higher benefit of lecanemab in males compared to females in CLARITY AD is probably due to a real sex effect*.

85 I. Gozes, J. Blatt and A. Lobyntseva, *Davunetide sex-dependently boosts memory in prodromal Alzheimer's disease*.

86 H.-Y. Lane, S.-H. Wang and C.-H. Lin, *Sex- and dose-dependent catalase increase and its clinical impact in a benzoate dose-finding, randomized, double-blind, placebo-controlled trial for Alzheimer's disease*.

87 J. Fang, P. Zhang, Y. Zhou, C.-W. Chiang, J. Tan, Y. Hou, S. Stauffer, L. Li, A. Pieper, J. Cummings and F. Cheng, *Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease*.

88 S. Haeberlein, P. Aisen, F. Barkhof, S. Chalkias, T. Chen, S. Cohen, G. Dent, O. Hansson, K. Harrison, C. Hehn, T. Iwatsubo, C. Mallinckrodt, C. Mummery, K. Muralidharan, I. Nestorov, L. Nisenbaum, R. Rajagovindan, L. Skordos, Y. Tian, C. Dyck, B. Vellas, S. Wu, Y. Zhu and A. Sandrock, *Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease*.

89 R. Buckley, J. Gong and M. Woodward, *A Call to Action to Address Sex Differences in Alzheimer Disease Clinical Trials*.

90 A. Miller, A. Desai, L. Roley, R. Goodwin, A. Nathaniel and T. Nathaniel, *The role of ethnicity, biological sex, and psychotropic agents in early and late onset Alzheimer's disease*.

91 J. Contador, A. PrezMillan, N. Guilln, J. Sarto, A. TortMerino, M. Balasa, N. Falgs, M. Castellv, S. Borregocija, J. JuncParella, B. Bosch, G. FerndezVillullas, O. RamosCampoy, A. Antonell, N. Bargall, R. SanchezValle, R. SalaLlonch and A. Llad, *Sex differences in earlyonset Alzheimer's disease*.

92 E. Sundermann, P. Maki, S. Reddy, M. Bondi and A., *Biegon and Alzheimer's Disease Neuroimaging Initiative, Women's higher brain metabolic rate compensates for early Alzheimer's pathology*.