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Understanding the impact of sex and gender in Alzheimer's disease: A call to action

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Abstract

Introduction: Precision medicine methodologies and approaches have advanced our understanding of the clinical presentation, development, progression, and management of Alzheimer's disease (AD) dementia. However, sex and gender have not yet been adequately integrated into many of these approaches.

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Conflicts of Interest

Dr. Aggarwal serves as consultant for Merck & Co., Inc. and Eli Lilly & Co. and receives research support from Eli Lilly & Co., Novartis, Amgen Inc., and Johnson & Johnson. Dr. Kantarci serves on the Data Safety Monitoring Board for Takeda Global Research & Development Center, Inc. Dr. Mormino served as a consultant to Biogen and Eli Lilly & Co. Dr. Maki received honoraria from Mylan. Dr. Mielke served as a consultant to Lysosomal Therapeutics, Inc. and Eli Lilly & Co. and receives unrestricted research grants from Biogen, Lundbeck, and Roche.

Methods: The Society for Women's Health Research Interdisciplinary Network on AD, comprised of an expert panel of scientists and clinicians, reviewed ongoing and published research related to sex and gender differences in AD.

Results: The current review is a result of this Network's efforts and aims to: (1) highlight the current state-of-the-science in the AD field on sex and gender differences; (2) address knowledge gaps in assessing sex and gender differences; and (3) discuss 12 priority areas that merit further research.

Discussion: The exclusion of sex and gender has impeded faster advancement in the detection, treatment, and care of AD across the clinical spectrum. Greater attention to these differences will improve outcomes for both sexes.

Keywords

Alzheimer's disease; Sex; Gender; Risk factors; Hormones; Biomarkers; Women; Men; Mild cognitive impairment; Menopause; Epidemiology

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes memory loss, cognitive deficits, and behavioral changes. More than 5.5 million Americans, including an estimated 5.3 million people aged 65 years and older, are currently living with AD dementia; approximately two-thirds of whom are women. AD dementia is the fifth leading cause of death in the United States (US) for women and the 8th leading cause of death for men [1]. The economic impact of AD is significant, costing an estimated $259 billion for the US health-care system in 2017. By 2050, AD is projected to cost more than $1.1 trillion dollars with fourfold increases both in government spending under Medicare and Medicaid and in out-of-pocket spending [1].

The hallmark characteristics of AD include the presence of extracellular senile plaques comprised of amyloid-b (Aβ) protein, intracellular neurofibrillary tangles (NFTs) made up of abnormally phosphorylated tau protein, and neurodegeneration [2]. Although AD neuropathology has been well defined, the underlying cause or causes of the disease remain debatable. Several theories have been suggested [3], including genetic susceptibility, the amyloid hypothesis, accelerated aging, the cholinergic hypothesis, neuroinflammation and immune dysregulation, neurovascular dysfunction, the mitochondrial cascade hypothesis, synaptic dysfunction, and environmental risk factors. There is considerable heterogeneity in AD pathology, the clinical presentation, and disease progression. Therefore, it is most likely that multiple pathways are involved and that the specific pathways affected differ across individuals.

Over the last decade, precision medicine methodologies and approaches have advanced our understanding of the pathophysiological changes involved in the development and progression of AD dementia and can inform the development of targeted interventions. However, sex and gender have not yet been integrated into precision medicine approaches. The exclusion of these factors have impeded faster advancement in the detection and

treatment of AD. Such advances are a key to optimize health-care utilization and the high costs associated with AD care.

Sex, in medical research, refers to biological and physiological differences between women and men, with sex chromosomes (XX vs. XY) and gonadal hormones primarily contributing to these differences at the cellular, organ, and systems level. *Gender* refers to a combination of environmental, social, and cultural influences on the biological factors in women and men. Gender is rooted in biology and shaped by environment and experience [4]. There is growing evidence to support that both sex and gender affect the etiology, presentation, and treatment outcomes of many diseases. Although, tremendous strides have been made in AD research over the past several years, limited attention has been given to sex and gender differences in AD, leading to significant knowledge gaps in research and a lack of awareness among the research community on sex and gender differences in AD [5]. To maximize the development of current and future treatments and interventions across the AD spectrum, sex and gender differences in AD must be better understood and measured [6–8]. By this, we mean that studies of female/male differences in AD should focus not only on biological sex but also on gender differences in factors such as education, caregiving, and other gender roles, as well as mental health factors where both biological and social factors contribute to female/male differences.

Building on this background, the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease, comprised of an expert panel of scientists and clinicians (Table 1), convened to review ongoing research and published literature related to sex and gender differences in AD to identify areas of need for future research. The aims of this review are to: (1) highlight the current state of the science in the AD field on sex and gender differences; (2) address knowledge gaps in assessing sex and gender differences in AD; and (3) discuss priority areas with respect to sex and gender differences that merit further exploration. While we understand that basic science is critical in contributing to our understanding of mechanisms underlying sex differences in AD and warrants continued attention, this review focuses explicitly on clinical research. The intent of the review is not to serve as a systematic review of the entire literature on sex and gender differences in AD, but rather to demonstrate that numerous clinical research studies point to the importance of considering biological sex when examining the epidemiology, clinical presentation, clinical course, and neurobiological manifestations of the disease. We also briefly describe the importance of recognizing caregiving as a role of the female gender that leads to women taking on a greater burden of the societal costs of AD. The overarching goal of the manuscript is to direct attention to this literature as justification for the importance of explicitly examining the effects of sex and gender in studies of AD, to understand the factors that contribute to inconsistencies in some areas of research, and to determine the robustness of sex and gender differences and their relevance to clinical practice.

1.1. Sex and gender differences in the frequency, prevalence, and incidence of AD

The terms used to describe sex differences for the number of people affected by AD are often used interchangeably (i.e., frequency, prevalence, and incidence) but mean different things. Understanding these definition differences is important in assessing sex differences

in disease burden. Based on a frequency count of all individuals with AD, more women than men are living with a diagnosis of AD. It is estimated that of the 5.3 million people aged 65 years and older with AD in the United States, 3.3 million are women, and 2.0 million are men [1]. The burden of AD also impacts women more substantially than men because two-thirds of caregivers are women, one-third of whom are daughters [1]. Women also have a greater lifetime risk of developing AD. Lifetime risk is defined as the probability that someone of a given age will develop a condition during his or her remaining life span [1]. The estimated lifetime risk for AD at age 45 is approximately one in five (20%) for women and one in 10 (10%) for men. An important contributor to this sex difference in both the frequency and the lifetime risk is that women live longer than men. Age is the strongest risk factor for sporadic AD and there are more women at older ages, when the development of AD is most likely. However, longevity does not wholly explain the higher frequency and lifetime risk in women.

When assessing the prevalence (total number with disease divided by total number of individuals in the population) or incidence (total number of individuals developing a disease in a given time period divided by the number of people at risk of the disease) of AD by sex, the results are conflicting and appear somewhat dependent on the time period and geographic region where the study was conducted. Several studies in Europe have reported a higher prevalence of AD among women [9]. However, a recent review and meta-analysis of over 22 studies across the world did not find that the prevalence of AD was significantly higher in women compared with men [10]. Notably, only 22 of 119 studies included in that meta-analysis reported findings by sex. Similarly, many of the early European studies suggested women were at greater risk of AD [11], with the exception of the Cognitive Function and Ageing Study from the UK, which found that men were at higher risk [12]. However, several studies in the United States [6], and around the world [10], have not reported a significant sex difference. Different theories for the geographical difference in the prevalence and incidence of AD by sex between the United States and Europe have been suggested [6, 13]. For example, in the early part of the 20th century, gender differences in educational and occupational opportunities varied between the United States and Europe. In contrast to the mixed literature on sex differences in AD, most studies of mild cognitive impairment (MCI), a prodromal stage of AD, suggest a higher prevalence and incidence among men [14, 15]

Notably, even if there is an overall lack of significant sex differences in the incidence of MCI or AD in the United States, it does not mean that sex or gender differences are not important. Heart disease is the number one cause of death for both women and men, but it is now known that there are sex differences in risk factors, symptoms, treatments, and mortality [16]. Better understanding of sex and gender differences has the potential to improve recognition of symptoms, prevention or stabilization of risk factors, and clinical outcomes. Similar to what has been observed in many other fields, there are an increasing number of studies demonstrating both sex and gender differences in the development, progression, diagnosis, and clinical presentation of AD [5, 6]. Below, we highlight some of these differences in an effort to improve the diagnosis and clinical outcomes in AD.

2. Differential risk factors for women and men

There are multiple scenarios by which sex and gender differences can affect disease risk: (1) risk factors that are equally common in women and men but have a stronger effect in one sex or gender group (e.g., apolipoprotein E [*APOE*] genotype); (2) risk factors that have a similar effect in women and men but are more common in one sex or gender (e.g., lower access to education in women); and (3) risk factors restricted to one sex (e.g., pregnancy, menopause). In this section, we first highlight sex differences in the risk factors for AD. We then describe potential gender-related sociocultural factors that can also differentially affect the risk and progression of AD in women versus men. Finally, we highlight sex-specific risk factors.

2.1. Examples of sex differences in risk factors for AD

2.1.1. Cardiometabolic risk factors—Several studies have identified modifiable cardiometabolic diseases including type 2 diabetes, metabolic syndrome, obesity, and other cardiovascular risk factors for the development and progression of AD [17]. Despite the well-known fact that the development, symptoms, and treatment of cardiometabolic diseases differ by sex [18], few studies have examined sex differences in cardiovascular risk factors for AD. Most studies to date have simply adjusted for sex in regression models. This is unfortunate because work on sex differences in the vasculature has shown that microvascular disease is a greater contributor to cardiovascular disease in women than in men, whereas obstructive coronary artery disease is a greater contributor in men than in women [19]. Moreover, women have a higher risk of diabetic complications than men, including myocardial infarction (MI), depression, and coronary heart disease, all of which are risk factors for AD [18]. Thus, while a diagnosis of hypertension, high cholesterol, and diabetes in midlife has been associated with a greater risk of developing AD for both women and men, the risk of AD for women with these factors may be greater than for men [20, 21]. New research is needed to understand whether the relationship between cardiometabolic factors and risk of AD differs by sex, and how this difference varies by age. Given that men typically develop cardiometabolic diseases at earlier ages than women (perhaps due, in part, to the protective effects of estradiol before menopause), additional research is needed to understand the interrelationship between sex differences in the timing of the risk factors and development of AD, and how this difference contributes to the age-specific distribution of AD.

2.1.2. Depression—While depression can be a symptom of AD in older adults, depression at midlife is believed to increase the risk of AD by as much as 70% [22]. Women have twice the risk of depression compared to men, a difference that emerges at puberty [23, 24], and worsens during the menopausal transition [25, 26]. Depression has implications for cognition across the life span given shared brain regions between mood and memory and shared etiologic pathways such as immune and stress hormone dysregulation. Some cohort studies found that elevated depressive symptoms were associated with AD only in men [27, 28]. Conversely, in the Women's Health Initiative Memory Study (WHIMS), clinically significant depressive symptoms were associated with a nearly twofold increased risk of MCI and dementia over a 5.4-year average follow-up in a sample of 6000 women [29]. A

past history of depression was also associated with a near doubling of the risk of dementia in WHIMS [29]. Another study found that depression was associated with hippocampal volume loss only in women [30, 31], while in WHIMS depressive symptoms were associated with prefrontal volume loss [32].

2.1.3. Sleep—Sleep and circadian rhythms disturbances are common among patients with and may impact the development of AD pathology as well [33]. The production and clearance of Aβ peptides is associated with the sleep-wake cycle, with wakefulness associated with Aβ production and sleep associated with Aβ clearance [34]. Subjective reports of poor sleep quality and short sleep duration as well as objective measures of high sleep fragmentation are associated with increased Aβ accumulation, poorer cognition, and increased risk of AD in older adults [35, 36]. Similar results are seen during midlife, where objective reports of short sleep duration, long sleep duration, and poor sleep quality are associated with poorer cognitive function [37]. Recent evidence suggests that disruption of sleep stage 3 (slow-wave sleep) in particular increases Aβ levels [38]. Interestingly, slow wave activity is greater in women than men across all ages [39, 40], although the effects of this difference on Aβ clearance is unknown. There is also a general decline in slow wave sleep with age [39–41]. In addition, the prevalence of sleep disturbances and sleep disorders can increase with age, with menopause being a particularly vulnerable time for women. For example, while sleep apnea is more prevalent in men, its incidence in women greatly increases after menopause [42]. Individuals with sleep apnea show cognitive decline at an earlier age than those without sleep apnea [43]. Taken together, current findings suggest that more research is needed to understand the relationship between sleep and AD risk, and whether that risk differs between women and men.

2.2. Examples of gender and sociocultural risk factors for AD

2.2.1. Education—Low socioeconomic status, education, and occupational attainment pose similar risk for AD in both women and men. However, in the past century, women have had fewer opportunities for higher education and occupational attainment. As a result, many more women than men are affected by this risk factor [6]. More recently, educational attainment for women has been higher than men in the United States [44]. The improvement in education and occupational attainment in women over the last few decades may be one explanation as to why the incidence of dementia may be declining more for women [45, 46].

2.2.2. Exercise—Physical activity at midlife is associated with a decreased risk of AD [47]. Women exercise less than men [48], and gender differences in parenting roles accounts for only some of this difference. The effect of exercise might also vary depending on estradiol level and menopausal stage, with greater benefits observed when estrogen levels are high [49].

2.2.3. Marital status—Compared with women, men who have never married or are widowed, have a greater risk of developing AD [20, 50, 51]. A potential reason for this consistent observation is that women have historically been responsible for the health-care of their family (e.g., getting offspring and partners/husbands to healthcare providers for regular checkups, assuring everyone has a healthy diet, and so forth), sometimes at the

expense of their own health. Single women, compared with single men, are also more likely to see a health-care provider and to engage in social activities, which are beneficial for cognition.

2.2.4. Caregiving for AD—Family caregivers for AD patients are usually either spouses or adult-children [52]. Women make up on average 60% of all family caregivers [52] and these rates are especially high for Hispanic and African American caregivers [53]. Women caregivers report a twofold higher level of caregiver burden compared to male caregivers [54]. Compared to sons, daughters of AD patients provided more routine assistance, experienced more guilt, were less likely to receive support from their spouses, and were more likely to leave the labor market to care for their parent [55, 56]. In contrast, sons were more likely to ask for help from other family members. When sons identified themselves as caregivers, it was relatively common that it was the son's wife who provided the care [56, 57]. Caregiving is associated with elevated levels of cortisol and impaired attention and executive function [58]. It has been hypothesized that spousal caregivers may be at higher risk of cognitive impairment or dementia than noncaregiver spouses in response to several psychosocial (e.g., depression, social isolation, and sleep problems), behavioral (e.g., exercise and diet), and physiological (e.g., metabolic syndrome and inflammation) variables [59]. More research is needed to better determine how gender differences in caregiver responsibilities may impact risk of AD.

2.3. Sex-specific risk factors for women

2.3.1. Hypertensive pregnancy disorders—Hypertensive pregnancy disorders (HPDs) are a major cause of maternal and fetal morbidity and mortality. These disorders affect approximately 12% of all pregnancies and include gestational hypertension, preeclampsia, eclampsia, chronic hypertension, and preeclampsia or eclampsia superimposed on chronic hypertension. Previous studies reported associations between HPD and subjective cognitive complaints [60, 61] or brain white matter hyperintensities on magnetic resonance imaginge [62–64]. However, these studies had small sample sizes and only assessed brain structure and cognitive function less than 10 years after the HPD. Recently, the long-term association between HPD (i.e., >10 years after pregnancy) and brain structure and cognitive function was assessed in a multiethnic study of 1279 women (mean age=61) enrolled in the Family Blood Pressure Project Genetic Epidemiology Network of Arteriopathy study [64]. Women with a history of HPD had greater brain atrophy decades after their pregnancies than women who had normotensive pregnancies. There was also a trend for more white matter hyperintensities in those with HPD. Given the increasing prevalence of HPD with increasing obesity and later maternal age, further research examining HPD and risk of AD is needed. There is also a need to determine whether there is a common underlying factor that increases the risk of both HPD and AD or whether HPD is, itself, an independent risk factor.

2.3.2. Menopause, hormone therapy, and cognition—A key determinant of sex differences in cognition and brain function is sex steroid hormones. Menopause is a universal event experienced by all women who live to midlife and beyond. Given that

women living today will on average spend one-third of their life in the postmenopausal stage, it is critical to consider menopause in brain function and AD.

2.3.3. Natural menopause and memory decline—Women demonstrate a decrease in verbal memory during the menopausal transition [65], a change that has been linked to alterations in hippocampal function associated with loss of estradiol [66, 67]. In some women, this decline appears to be temporary, as two longitudinal studies show a decline in verbal memory during perimenopause, but not during postmenopause [65, 68]. Recent cross-sectional studies, however, found impairment in verbal memory among postmenopausal women but not among perimenopausal women [66, 67, 69].

2.3.4. Risk of initiating hormone therapy late in life—There is considerable confusion about whether estrogen containing hormone therapy (HT) is protective or harmful in women with respect to the development of AD. Findings from WHIMS showed that combination estrogen plus progestin therapy in women aged 65 years and older doubled the risk of dementia [70, 71]. Analysis of the data from WHIMS showed that the most serious adverse events, including those on brain and cognition, occurred in women who began with low cognitive function at baseline [70]. These findings suggested that initiating HT at an older age and among women whose cognitive performance is atypically low may have adverse consequences. The relevance of these findings to clinical practice was brought into question because the very large majority of women initiate HT earlier in life, during the menopausal transition. Furthermore, these findings were at odds with findings from a recent Women's Health Initiative (WHI) publication on the effects of HT on mortality over 18 years of cumulative follow-up [72]. Women randomized to estrogen therapy had a significantly lower risk of dying from AD or dementia than women randomized to placebo. This effect was not observed in women randomized to estrogen plus progestin therapy in the WHI. The number of cases was too small to determine whether the effect was dependent on timing of the initiation of HT in relation to menopause. The mortality findings need to be interpreted with caution because the cause of death was reported by National Death Index and in some cases next of kin, whereas dementia cases were prospectively adjudicated in WHIMS. On the other hand, the smaller number of dementia cases in WHIMS (n=237 dementia cases) compared with WHI mortality study (n=758 cases) leads to less statistical power in WHIMS, and a sizeable proportion of referrals for dementia determination in WHIMS was not adjudicated. Currently, there are insufficient data to determine the effects of menopausal HT on late-life dementia.

Observational data show that women who initiate HT early in the menopausal transition or at a younger age have a lower risk of AD than women who initiate HT later [73–75]. This pattern is consistent with the critical window hypothesis of HT, which suggests that early initiation of HT in relation to the menopausal transition confers greater cognitive benefit than initiation later in life [76, 77]. In contrast, a recent population-based study of 489,105 Finnish women showed that the risk of death from AD was reduced by 15%−19% in women who used HT for at least 5 years. Risk of death from vascular dementia was reduced from 37% to 39% regardless of the length of exposure or timing [78]. One benefit of the Finnish data is that compared to US data, Finnish data appear to be less influenced by the healthy

user bias, the tendency of women who go on using HT to be healthier and better educated than other women.

2.3.5. Effects of HT on cognitive function in the early postmenopause—High-quality clinical trials provide reliable evidence that HT early in the postmenopausal period does not confer cognitive benefit but is safe for cognitive function. Specifically, three large trials demonstrated no immediate or enduring adverse effects of HT on cognition when HT was initiated within 5 years of the final menstrual period [79–81]. One of those trials focused on women from the WHI who were aged 50–59 years (mean age=53) at randomization and found no negative cognitive effects when women were tested 14–15 years later. Another included a site-specific neuroimaging study which indicated that Aβ deposition was lower in *APOE* ε4- positive women randomized to receive estradiol compared with those randomized to receive placebo [82]. It is possible that the effect was observed only in *APOE* ε4-positive women, because *APOE ε*4 carriers have greater Aβ deposition at an earlier age than *APOE ε*4 noncarriers. Unfortunately, although the primary indication for HT is hot flashes, none of those studies selectively enrolled women with bothersome vasomotor symptoms. Some evidence demonstrates that vasomotor symptoms are associated with memory deficits [83, 84]. Overall, there is no support for a "critical window" of HT in the early postmenopausal period but that hypothesis has not been tested in symptomatic women or women earlier in the menopausal transition. Studies of oral contraceptives or HT in perimenopause are warranted given that the memory decline that occurs during the menopausal transition emerge in early perimenopause and appear to resolve in the early postmenopausal period [65, 68].

2.3.6. Gynecological surgeries—Most studies [85–93], but not all [94, 95], have shown that earlier age at menopause (natural or surgery-induced) is associated with an increased risk of cognitive decline and dementia. Notably, the increased risk of cognitive impairment and dementia did not vary by indication for the oophorectomy and was eliminated by estrogen therapy that was initiated after the surgery and continued up to 50 years of age or longer [85]. Collectively, these studies suggest that bilateral oophorectomy may be a risk factor for cognitive decline and dementia. Such a conclusion is supported by findings that an earlier age at surgical menopause was associated with a greater burden of neuritic plaques at autopsy [93]. However, the women who underwent these surgeries can differ from other women in ways that put them at higher risk of cognitive impairment and dementia independent of the surgery [13]. For example, women with adverse childhood experiences or adult abuse were found to be at increased risk of undergoing bilateral oophorectomy before menopause [13], and early childhood trauma has been associated with an increased risk of late-life dementia [96]. It may be that early oophorectomy interacts with such risk factors to influence risk of dementia. More generally, well-controlled studies measuring AD pathology *in vivo* (cerebrospinal fluid [CSF] positron-emission tomography [PET]) in women with early surgical menopause are warranted to better interpret the epidemiological findings.

2.3.7. Neurobiological model of aging and menopause—Both clinical and basic science studies provide a theoretical framework for understanding menopause as a female-

specific risk factor for AD. Specifically, it has been proposed that perimenopause is a bioenergetic transition state characterized by a decline in mitochondrial function and a change in fuel source from glucose to lipids which in turn could lead to remodeling of the brain, loss of synaptic spines (especially in the hippocampus), and ultimately neurodegeneration [97–103]. In support of this view are neuroimaging data demonstrating that compared with premenopausal women, perimenopausal and postmenopausal women show AD-like reductions in glucose metabolism, and these reductions are related to platelet mitochondrial activity [104].

3. Clinical presentation of AD

3.1. Sex differences in verbal memory: Implications for AD diagnosis

The tests most frequently used to diagnose AD are tests of verbal memory, memory for word lists, stories, and other verbal materiasl. There is a lifelong female advantage in verbal memory [105], which can be partially explained by sex steroid hormones, particularly estradiol [67]. Studies in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort show a female advantage in verbal memory not only during normal cognitive aging but also during amnestic mild cognitive impairment even though women's level of disease burden - as measured by hippocampal atrophy, brain hypometabolism, and cortical Aβ deposition – is similar to men, even after adjusting for *APOE* genotype [106–108]. At high levels of disease burden, the female advantage was eliminated. Those findings may indicate that the female advantage in verbal memory serves as a form of cognitive reserve, allowing women to sustain cognitive performance in early disease stages despite moderate levels of brain pathology. While the female advantage may be functionally beneficial, the downside is that it may delay amnestic MCI diagnosis so that women have a more severe burden of disease at the time of diagnosis and decline rapidly thereafter, limiting the opportunity for early intervention. This framework might also explain why women show a more rapid decline across a wide range of cognitive abilities after being diagnosed with AD [109–111]; if women are diagnosed at a more advanced stage, then they can be expected to show a more rapid rate of deterioration. This hypothesis is currently being tested in other cohort studies to determine if results generalize outside of ADNI and to determine if results vary by *APOE* genotype, as ADNI has a higher frequency of individuals with an *APOE ε4* allele compared with the general population. If replicated, this body of work suggests a need for alternative approaches to improve early detection in women, including the possible use of sex-specific cutoff scores to detect impairment in verbal memory and/or the use of memory tests that do not show a sex difference.

3.2. Sex and gender differences in biomarkers: Neuroimaging, CSF, and autopsy studies

New neuroimaging and CSF biomarkers show promise in elucidating the influence of sex on AD pathophysiology. Validated AD biomarkers used commonly in clinical trials comprise three distinct categories: (1) biomarkers of Aβ deposition, which include decreased CSF Aβ42 and elevated Aβ ligand uptake on PET; (2) biomarkers of neurofibrillary tangle tau pathology, which include elevated CSF phosphorylated tau and elevated NFT-tau ligand uptake on PET; (3) biomarkers of neurodegeneration which include decreased glucose

metabolism on F-18 fluorodeoxyglucose PET, structural magnetic resonance imaging measures of atrophy in the temporoparietal cortex, and elevated CSF total tau [112].

Biomarkers define the preclinical stage of AD [113, 114], the stage for optimal intervention to prevent or delay MCI due to AD and ultimately AD [113]. Identifying sex differences in AD biomarkers during the preclinical stage is critical for the planning of prevention trials, but surprisingly little is known. In a cross-sectional, population-based cohort of cognitively normal individuals (50 to 89 years), Aβ, NFT-tau burden, and neurodegeneration all increased with age, but no sex difference was observed [115]. Longitudinal data from ADNI indicate that women with MCI tend to show greater atrophy rates and greater cognitive and clinical decline than men [110, 111, 116]. For example, rate of progression in the clinical rating scale [106], global brain atrophy [107, 108] , and hippocampal volume loss [108] was faster for women with MCI compared with men with MCI, and the patterns of gray matter loss have been shown to differ between the sexes [117]. To support these ADNI findings, serially measured AD biomarkers in community or population-based samples may clarify the differences in rates of decline in women and men.

Previous autopsy studies have demonstrated that AD pathology is more likely to be expressed clinically as dementia in women than in men. In a group of older persons from the Religious Orders Study, who underwent detailed clinical evaluations proximate to death, the association between AD pathology and clinical AD was substantially stronger in women than in men [118]. Using a composite measure of AD pathology that ranged from 0 to 3, each additional unit of pathology increased the odds of clinical AD nearly threefold in men compared to more than 20-fold in women. This effect was observed for both neuritic plaques and NFTs. The findings were similar when change in cognitive function was used as the outcome measure. These data provide strong evidence that women are more susceptible to the clinical manifestation of AD than men. Although the mechanisms underlying the finding were not certain, the authors suggested that the stronger association in women could have been due to a relative lack of some protective factor, such as the estrogen deficiency of postmenopausal women, which could increase vulnerability to AD pathology. Other studies have since reported similar findings with the same amount of pathology yielding a more severe clinical effect in women than in men [119, 120].

3.3. Sex and gender differences in biomarkers: Genetics

3.3.1. The *APOE* ε4-sex interaction on AD—The ε4 allele of the *APOE* gene is a major genetic risk factor of late-onset AD dementia [121] and is consistently linked with abnormal accumulation of the Aβ protein [122]. The apoE protein is involved in the transport of cholesterol and other lipids in the periphery of the brain. The apoE4 protein has been shown to be less effective at Aβ clearance [123], and contributes to a diminished response to neuronal injury compared to the apoE2 and apoE3 proteins [124]. An analysis of nearly 58,000 participants showed sex differences in the risk of AD dementia and MCI by *APOE* genotype [125]. Among persons aged 65–75 years with the *APOE ε3/ε4* genotype, the risk of AD dementia is fourfold higher in women than that in to men. Similarly, among those aged 55 to 70 years with the *APOE ε3/ε4* genotype, the risk of MCI is 43% higher in women than that in men. Although the mechanisms underlying the interaction between sex

and the *APOE* genotype remain unclear, results across research groups have suggested that *APOE* ε4 females may show greater levels of AD pathology, more compromised brain network integrity, and/or accelerated longitudinal decline for a given level of AD pathology [126–128].

3.3.2. Women APOE ε4 carriers have worse longitudinal performance than men—In an analysis of over 5400 clinically normal participants, women who were *APOE* ε4 carriers had an elevated risk of progression on the Clinical Dementia Rating scale compared with both *APOE* ε4 men and *APOE* ε4-negative women; this effect was also observed in analyses restricted to *APOE ε3/ε4* carriers. Although an analysis of MCI patients (N>2500) found no sex by *APOE* ε4 (homozygote and heterozygotes combined) interaction in progression to AD dementia, an analysis restricted to *APOE* ε4 heterozygotes revealed a similar sex by *APOE* ε4 interaction [126]. Several studies have shown that *APOE* ε4 women had a faster decline of cognitive function compared to either women noncarriers or men of any genotype [129, 130].

Because women with an *APOE* ε4 allele are at increased risk of developing AD compared with women without ε4, more work is needed to clarify whether *APOE* status modifies the effects of female-specific risk factors for AD. This approach has been undertaken in studies of HT and AD risk, but without clear consensus. Some studies suggest that the effects of HT on cognition in women is influenced by *APOE* genotype, with benefits of HT observed in *APOE* ε4 noncarriers only, whereas other studies suggest that HT reduces AD risk in *APOE* ε4 carriers [131] or that HT reduces AD in both carriers and noncarriers [132, 133].

Overall, these data suggest that the *APOE* ε4 allele interacts with sex to influence risk of AD dementia. The increased risk among women may be due to multiple underlying mechanisms, including direct effects of apoE on AD pathology and on individual trajectories of decline for a given level of pathological burden. An important limitation regarding the observed *APOE*-associated sex differences in AD, is evidence of earlier mortality of *APOE* ε4 men that results in a selective *APOE* ε4 survival bias for women [134]. Future research is also needed to examine the sex-specific differences in the influence of the *APOE* ε4 over the life span. For instance, it is possible that the interaction between sex and *APOE* ε4 occurs during menopause, at a time when the risk of Aβ accumulation first begins to increase among *APOE* ε4 individuals [135]. However, most studies investigating dementia risk have examined older ages (>65), making it difficult to isolate the potential impact of sex during midlife.

4. Future directions: Priority areas with respect to sex and gender differences that merit further exploration

Reviewing the evidence presented in this review, the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease made a consensus-based list of the 12 highest priorities in sex and gender differences in AD research that warrant further attention (Table 2). These priority areas require interdisciplinary, cross-institutional approaches with strong support from academia, industry, government, and the public. The Society for Women's Health Research will capitalize on this information in its efforts to advocate for

greater attention to sex and gender differences in AD, with the ultimate goal of improving diagnosis, clinical outcomes, and health equity for both sexes.

At the epidemiological level, it is important to evaluate the extent to which findings of sex and gender differences in AD are due to differences in longevity, survival bias, and comorbidities. Biological and sociocultural factors can differentially affect the risk and progression of AD in women versus men. Biological hormonal factors are of particular interest, because the extant literature suggests that oophorectomy, menopause, and androgen-deprivation therapy are associated with deleterious cognitive changes and may represent sex-specific risk factors for AD. Indeed sex steroids play a key role in sex differences in the brain, yet relatively little is known about the role of endogenous and exogenous estradiol in the pathogenesis of AD. In light of discrepancies in the clinical literature, further work on the influence of estrogens and HT on brain function and AD risk is also warranted as a sex-specific risk factor.

Most risk factors for AD are evident in both sexes (*APOE* genotype, cardiovascular disease, and depression), but to date, most studies have covaried for sex when examining these factors. In genetic studies, sex differences are studied more commonly given the strong evidence that sex modifies the association between *APOE* genotype and AD risk. With this example, it would be beneficial to include exploratory analyses of potential sex differences in other AD risk factors. Given that some AD risk factors and comorbidities are modifiable, determining the extent to which sex differences contribute to differential risk may present opportunities for new therapeutic avenues. Similarly, further research is needed on how gender-related factors such as health perceptions, risk behavior, social and work-related stressors, patient-provider relationships, and adherence to therapy impact AD risk, diagnosis, therapeutic response, and course of disease.

There is a need for continued evaluation of sex differences in AD progression and the trajectory of change in cognitive function, neuroimaging, CSF, and blood-based biomarkers of AD. Identifying sex differences in AD biomarkers and how biomarkers change across the life span, particularly at earlier ages, is critical for the planning of prevention trials. Sex differences must also be investigated in diverse populations to determine potential differences as a function of sex *and* race or ethnicity. For example, African-Americans are two to three times more likely to be diagnosed with AD or related dementias [136], but whether or not this increased risk is uniform across African-American women and men has not been explored. Such work is critical to inform understanding of the factors involved in the secular changes (e.g., societal, political) and geographical variation in estimates of sex differences in AD. As the global burden of AD increases, studies of gender differences in caregiving and how the burden of caregiving influences AD risk take on greater importance as well.

Sex and gender differences should be a priority in the development of AD therapeutics from preclinical (e.g., inclusion of female animals and consideration of hormonal states) to clinical studies. To fully investigate the influence of sex and gender, we must develop a methodological framework through which we can analyze these influences, and one that also allows for interpretation of the trial results (e.g., sex differences in verbal memory function).

As the field shifts toward early detection and primary and secondary prevention, sex and gender must be considered in trial design. For example, women have an advantage in verbal memory, which is frequently tested to diagnose AD, and this advantage may mask the signs of early AD and delay diagnosis until a more advanced stage of disease. Diagnostic criteria and tools may need to be optimized for each sex with the goal of improving detection and the measurement of clinical progression for both sexes.

Few studies have examined sex differences in response to current approved and investigational medications. There are opportunities to engage in sex and gender data mining in clinical trials both retrospectively and prospectively, recognizing that with limited power the goals might be to generate effect size for future studies. Clinical trial data could also be examined to contribute to the understanding of sex differences in the clinical and pathological course of disease. Finally, understanding sex and gender differences in the clinical treatment of AD, including differences in provision of care and use of nursing home care, will lead to a better understanding of the differential needs of women and men across the disease continuum.

The field of AD research could benefit from lessons learned in other medical fields. For example, calls to evaluate potential sex differences in primary prevention of cardiovascular disease were validated when the Women's Health Study findings revealed that aspirin did not reduce the risk of MI in women [137, 138]. Indeed, meta-analyses of aspirin for the primary prevention of cardiovascular disease suggest that aspirin significantly reduces the risk of stroke but not MI in women but in men reduces MI but not stroke [139]. Age appears to be a critical determinant of these sex differences, as women aged 65 years and older show reductions in MI and stroke with aspirin therapy whereas younger women do not. Thus understanding sex differences in clinical response across the age continuum is critical in evaluating the efficacy of therapeutics in other fields. A similar approach in the field of AD has the potential to improve health for both women and men.

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Table 1.

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Table 2.

Research priority areas in sex and gender differences in AD clinical research

Further investigation of:
1. The extent to which findings of sex and gender differences in AD are due to differences in longevity, survival bias, and comorbidities
2. Potential sex-specific risk factors for AD (e.g., oophorectomy, menopause, pregnancy, androgen-deprivation therapy, and testosterone loss) across the lifespan
3. The influence of estrogens and hormone therapy on brain function and AD risk in light of discrepancies in the clinical literature
4. Potential sex differences in genetic risk factors for AD (e.g., *APOE*, x-linked, common variants, autosomal dominant mutations, etc.)
5. Sex and gender differences in AD risk factors that are observed in both sexes (e.g., cardiovascular disease, diabetes, education, depression, etc.) across the lifespan
6. Sex differences in AD progression and the trajectory of change in cognitive function, neuroimaging, CSF, and blood-based biomarkers of AD
7. The effects of sex differences in brain development on sex differences in brain aging and, ultimately, AD pathology and dementia
8. The effects of sex and gender in risk factors, disease progression, and biomarkers in racial and ethnic subgroups, especially in African-Americans and Hispanics/Latinos, and how this informs differential risk
9. The factors involved in the secular changes (e.g., societal, political) and geographical variation in estimates of sex differences in AD
10. Gender differences in caregiving and how the burden of caregiving influences AD risk
11. Sex and gender differences in developing AD therapeutics, from preclinical to clinical studies, and in the design of clinical trials
12. The effects of sex and gender differences on the clinical detection, diagnosis, management, and treatment of AD for both sexes