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Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative

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Abstract

More than 5 million Americans are living with Alzheimer's disease (AD) today, and nearly two-thirds of Americans with AD are women. This sex difference may be due to the higher longevity women generally experience; however, increasing evidence suggests that longevity alone is not a sufficient explanation and there may be other factors at play. The Alzheimer's Association

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convened an expert think tank to focus on the state of the science and level of evidence around gender and biological sex differences for AD, including the knowledge gaps and areas of science that need to be more fully addressed. This article summarizes the think tank discussion, moving forward a research agenda and funding program to better understand the biological underpinnings of sex- and gender-related disparities of risk for AD.

Keywords

Alzheimer's disease; Neurodegeneration; Risk factors; Women; Sex biology; Estrogen; Hormones; APOE

1. Introduction

Women are at the epicenter of the Alzheimer's disease (AD) epidemic. Two-thirds of the >5 million Americans living with dementia due to AD are women, and women account for about 65% of the >15 million unpaid caregivers of individuals with AD [1]. As real a concern as breast cancer is to women's health, women in their 60s are about twice as likely within their lifetime to subsequently develop AD as they are to develop breast cancer [2].

In 2010, the Alzheimer's Association partnered with the *Shriver Report* to publish "A Women's Nation Takes on Alzheimer's Disease", a book that highlighted the disproportional number of women living with and affected by AD [3]. This partnership amplified the public health risk awareness of AD for women. Furthermore, the Alzheimer's Association's 2014 Facts & Figures reported for the first time the disproportionate impact of AD on women [2], particularly those aged 65 years and older who are nearly twice as likely to develop AD compared with similarly aged men. Although AD represents a significant problem for the entirety of society, the impact of this disease and the unique burden on women in terms of emotional, physical, and financial factors merit careful consideration.

Reasons for the higher frequency and age-specific prevalence of AD among women at older ages are not well understood. Increasing age is the most influential known risk factor for AD. Thus, the higher frequency of AD in women may be partly explained by the fact that women live longer. Indeed, greater female lifespan is seen across all socioeconomic classes and is recapitulated throughout much of other mammalian species as well as in animal and cell-based studies. However, it is possible that increased longevity alone may not account for the higher prevalence in women.

Women with AD or other neurodegenerative diseases may have increased survival compared with men, independent of diagnosis [4]. The reasons for this possible sex difference are not clear and suggest that there may be other confounding factors for higher prevalence in women [5,6]. Prevalence is determined by both the rate of disease occurrence in a population (incidence) and the duration of survival after disease onset [4]. In general, women with AD seem to live longer with the disease than do men with AD, following a diagnosis; however, there are notable exceptions that do not fit this same trend [7–9]. Although it is accepted that AD prevalence is greater in women than in men, epidemiologic studies examining sex differences in the incidence of AD suggest a different picture. Most

studies in the United States report no significant difference in incidence between men and women, for example, the Baltimore Longitudinal Study of Aging [10], the Mayo Clinic Study of Aging [11], the Framingham Heart Study [12], and the East Boston study [4]. Other studies, including the Cache County Study (Cache County, Utah) [13] in the United States and European studies such as the PAQUID project [14], the Rotterdam Study [15], the Kungsholmen Study [16], and the Cambridge Project for Later Life [17], report a markedly higher incidence in women than in men after about age 80 years, with incidence before age 80 years either modestly greater in men than women or not different for men and women. The Mayo Clinic Study of Aging also found that the rate of progression from mild cognitive impairment (MCI) to AD was higher in men compared with women aged 70 to 79 years, but higher in women than men after age 80 years [18]. These complex patterns warrant further consideration of sex and gender differences in AD.

Although differences in the frequency and prevalence of AD for men and women were briefly examined, the think tank discussion primarily focused on the biological underpinnings and differences between men and women that may contribute to the disease-related pathophysiological changes. Regardless of any sex differences in the prevalence of AD, it is important to consider differences in risk for men and women. Indeed, multiple factors may contribute to the differential development and progression of AD between men and women, including biological factors (i.e., sex differences) such as chromosomal, epigenetic, or hormonal differences and psychosocial and cultural factors (i.e., gender differences) such as access to education and employment [19]. Education is a known, key mediator of cognitive reserve/resilience, and it could be that cognitive reserve/resilience effect may underlie the observed differences between men and women. Although there are increased efforts for equity across genders for education access, for instance, the population older than 65 years today had significant differences in educational attainment [20]. Obesity, diabetes, and depression are all factors that are associated with an increased risk of AD but also differ by sex across the lifespan in their prevalence, symptom presentation, treatment response, and mortality. Similarly, cardiovascular disease is associated with an increased risk of AD but occurs approximately 10 years later in women than men. Selective survival may be important because men who live to older ages are more robust and potentially at lower risk of developing AD [21]. To date, there is no clear sense of quantitative contribution for each of these factors. Thus, it is critical to increase knowledge of sex- and gender-related differences that could lead to both an increased understanding of the pathophysiology of AD and potentially inform development of novel therapies for both sexes.

In May 2015, the Alzheimer’s Association convened scientific experts to explore these questions, discuss the conflicting data, and determine the biological, epidemiologic, and societal factors that contribute to sex differences in the development and progression of AD. This article summarizes discussions focused on the state of the science and level of evidence around sex-related differences for AD, including identification of pertinent knowledge gaps and areas of science that need to be more fully addressed.

2. Biological mechanisms suggested in sex differences for vulnerability to AD

Emerging evidence suggests that there are biological differences that could contribute to life course differences in AD vulnerability. Sex biology differences in brain development are particularly germane to the development of AD. These include neuroanatomical and neurochemical as well as psychological, behavioral, and cognitive differences. Neuroanatomical differences range from the size of different regions of the brain to differences in synaptic patterns and neuronal density [22]. The male brain is about 10% larger than the female brain across the lifespan [23], and the proportion of white matter and gray matter differs between men and women [24]. Furthermore, among cognitively normal adults, brain volume tends to decline faster in men than in women [25], whereas in individuals with MCI and AD, brain volume declines faster in women than men [26]. There is now compelling evidence for sex differences in longitudinal patterns of cognitive aging, demonstrating faster rates of decline in men relative to women across a number of domains, and none in which women decline faster than men [27]. Education is a known mediator of cognitive reserve and could be contributing to the education effects on sex differences. This apparent enhanced resilience in normal aging for women and the relationship to AD or altered disease-related biological pathways represent important areas for further investigation.

Brain differences between men and women may also play a role in contributing to biological differences of disease-related pathways. For instance, it is possible that increased white matter proportions in the female brain may also contribute to observed differences in brain connectivity between men and women, which in turn are likely to contribute to differences in cognitive impairment. In addition, the accumulation of AD pathology, particularly β-amyloid (Aβ) accumulation, appears to differ by sex in both human and animal studies, although the results of these studies have been somewhat conflicting [28]. Taken altogether, these lines of evidence suggest that there are fundamental differences between the brains of men and women structurally that may play a contributing role in differential disease-related biology in AD.

2.1. The role of sex chromosomes

Animal studies have begun to elucidate some of the biological reasons underlying the increased longevity of women. For example, Dubai et al [29] described experiments in AD mouse models designed to isolate and establish the unique effects of sex chromosomes and gonads on aging and AD. Depletion of the gonadal steroids testosterone and estradiol is a fundamental aspect of human aging; however, levels of these hormones remain relatively stable in aging mice [30]. To overcome this problem, investigators depleted hormones in mice engineered to have female chromosomes but male sex organs (testes) as well as male mice with female sex organs (ovaries). When these mice overexpressed human amyloid precursor protein (APP)—one of several available AD mouse models—the male genotype mice died faster regardless of whether they had male or female sex organs, suggesting that the sex chromosomes may contribute to AD-related brain changes in APP transgenic mice.

There has been little work to investigate whether the sex chromosomes code for any AD-related genes of interest. About 1600 genes are encoded on the X chromosome, including genes for the androgen receptor and proteins associated with mitochondrial dysfunction. The smaller Y chromosome includes genes that code for male-related sexual characteristics and innate immunity [31]. Yet only a tiny fraction of findings from genome-wide association studies (GWAS) pertains to the X and Y chromosomes [32]. Further investigation to identify potential risk genes on the X or Y chromosomes may give new insight into the differential biological pathways involved in disease pathogenesis.

2.2. APOE ε4 and increased risk of AD in women

Although few GWAS studies have examined genes on the X and Y chromosomes, they have identified >20 genetic loci on autosomal chromosomes that are linked to an increased risk of AD [33]. *APOE* ε4 is the most well-characterized risk gene for AD identified to date. Presence of an *APOE* ε4 allele significantly increases the risk of AD and lowers the age of onset in a dose-dependent fashion based on sex [34,35]. Notably, women who carry one or two *APOE* ε4 alleles have a higher age-specific odds ratio of AD than men with the same *APOE* genotype although this effect is reduced after age 85 years [36]. Women with an *APOE* ε4 allele are also significantly more likely to convert from MCI to AD compared with men [37]. Multiple studies, ranging in size and significance, have suggested that women, compared with men, who are *APOE* ε4 carriers show more changes in default mode network connectivity [38], increased brain hypometabolism and greater brain atrophy [39], as well as worse memory performance [40]. Among individuals with MCI who were *APOE* ε4 carriers, women had significantly higher cerebrospinal fluid levels of total tau, a biomarker associated with neurodegeneration, compared with men [37]. Based on evidence to date, it is unclear if this same comparison would also hold for male and female non– *APOE* ε4 carriers. Consistent with these human studies, in mice expressing human *APOE* in brain, 6-month-old female mice expressing ApoE4 showed memory impairments not seen in age- and genotype-matched male mice or in mice expressing ApoE4 or murine ApoE-deficient female mice [41]. At 18 months of age, the cognitive impairments in ApoE4 female mice became more pronounced and learning impairments were seen as well [42].

Differences in telomere length have also been reported to be linked to biological sex and *APOE* ε4 genotype. In comparison to noncarriers, women carrying the *APOE* ε4 allele tend to have shorter telomeres—the caps on the ends of chromosomes that prevent them from recombination or degradation—than those of men in the same study. Telomere length reflects cellular age and has been linked to neurodegeneration and cognitive decline in the elderly [43]. Some studies suggest that the sex difference in telomere length may be driven by estrogen [44]. Indeed, in a 2-year study of high-functioning postmenopausal women, *APOE* ε4 carriers exhibited telomere shortening compared with noncarriers, hormone replacement (HR) prevented this decline in telomere length among *APOE* ε4 carriers, but not noncarriers [43]. It is unclear how *APOE* ε4 may contribute to disease-related biology, whether it increases risk or it has a biological interaction in disease-related pathways.

Additional roles that APOE may play in the context of stress and depression are expounded in Section 2.2, further suggesting that it plays a differential role in sex differences for disease vulnerability.

2.3. Hormones and AD

Sex hormones may play important roles linked to sex vulnerability to aging and to AD. With regard to estrogen replacement in women, there is an enigmatic gap between the results of animal models and those in randomized control trials in humans [30]. In animal models, estrogen may be neuroprotective in the normal brain through a myriad of possible mechanisms [28,30,45–48], including increasing hippocampal dendritic spine density [49], long-term potentiation [50], and neurotransmitters [51]; it may also be protective in the context of AD-related toxicity including decreasing cell death [52] and reducing Aβ accumulation and tau hyperphosphorylation [45]. Although many observational studies in women suggest that estrogen replacement improved aspects of cognition, the randomized, prospective clinical trials to test the hypothesis including the Women's Health Initiative Memory Study (WHIMS) and the Kronos Early Estrogen Prevention Cognitive and Affective Study have not shown benefit [30,53–57]. Reasons for the discrepancies require further investigation.

Androgens have also been suggested to be protective against Aβ-induced pathology [58–60], and age-related testosterone depletion is associated with AD [61]. In animal models, testosterone, dihydrotestosterone 40, and selective androgen receptor modulators [62] have been shown to improve cognitive performance in mice lacking mouse APOE and expressing ApoE4 in brain, whereas male mice expressing ApoE4 were more susceptible to cognitive impairments after treatment with androgen receptor blockers [63]. Consistent with these data, the effects of ApoE4 on cognition were modulated in mice expressing a dysfunctional androgen receptor, testicular feminization mutants (*tfm*) [64]. Sex differences in the distribution of estrogen receptors may also contribute to sex dimorphisms in cognitive and behavioral skills, as well as sex differences in brain structure, metabolism, synaptic plasticity, and the organization of neural circuits [65]. Differential exposure to hormones during development and adulthood may also contribute to physiologic outcomes relevant to disease.

Hormone studies with rhesus macaque monkeys mimic the hormonal changes in women throughout the life course and have reported that there are modest sex-based differences in how hormones affect cognitive decline as the monkeys age [66]. Specifically, female rhesus monkeys undergoing menopause experienced somewhat greater declines in executive function than did similarly aged males. Furthermore, female monkeys with surgically removed ovaries that received therapy of estradiol demonstrated significantly improved brain function, as measured by synaptic health [67]. More research is needed to understand the impact of hormone level fluctuation in relation to cognition at specific stages.

Although both sexes experience hormonal declines in midlife, the loss of estrogen in women during menopause is more abrupt than the loss of testosterone in middle-aged men [28]. Although women experience changes in hormonal levels throughout their life course, in recent years there has been a particular focus on the time period called perimenopause

[68], during which the female body makes the natural transition toward menopause and experiences significant alterations and disruptions in hormone levels, especially estrogen and progesterone [69,70]. These hormonal changes lead not only to reproductive senescence but also to a wide range of neurologic symptoms, including disruptions in temperature regulation (i.e., “hot flashes” or “flushes”), sleep, cognition, and mood [71]. For example, studies suggest that the loss of estrogen during perimenopause may impact verbal memory [72].

Mechanistically, these neurologic symptoms may be related to metabolic dysregulation in the brain brought about by a decline in circulating estrogen [73]. Rodent studies suggest that estrogen regulates the bioenergetics system in the brain through the estrogen receptor network, enabling mitochondria to convert glucose into energy [71,73,74]. In mice, declining estrogen levels during menopause force a shift to a less efficient energy source—ketone bodies [75]. This process represents a kind of “starvation mechanism,” and its results appear to be irreversible. Furthermore, the loss of estrogen has also been linked to increased levels of A3, an effect which is modulated by *APOE* [76]. The role that metabolic pathways may play is discussed in Section 2.4; however, the degree to which these relationships are also observed in humans requires further study.

Animal studies show that perimenopausal declines in energy metabolism measures are associated with a decrease of synaptic activity in the brain, suggesting a possible intersection of hormonal changes with neuronal plasticity [77]. Although all women go through perimenopause, only approximately 80% experience the associated side effects, most commonly hot flushes, but also cognitive dysfunction, insomnia, depression, headaches, and disruption of circadian rhythms [68]. Epidemiologic studies suggest that in cases when women experience “hot flushes” in the context of one or more neurologic disorder(s), they are also at greater risk for future cognitive decline, including AD. Other elements may also play a role in whether perimenopause may influence dementia vulnerability, including ethnicity, baseline cognitive health, and lifestyle factors [50,71,73,78].

As mentioned earlier, several studies conducted in the 1980s and 1990s suggested that postmenopausal estrogen therapy might protect menopausal women from cognitive aging [79]. However, subsequent results from the WHIMS and other studies showed that rather than being protective, equine estrogen plus progestin therapy resulted in lower cognitive function among older women, particularly those with signs of cognitive decline at the beginning of the trial [55,57]. It was also associated with increased risk for dementia and smaller brain volumes [80,81]. In an attempt to resolve this discrepancy, it was hypothesized that estrogens might only be neuroprotective during a critical time period around the beginning of menopause [82]. Basic research supported this hypothesis [83]; however, three major randomized controlled clinical trials of hormone therapy given nearer the time of the menopausal transition have found that hormone therapy has no impact on cognition [56,57,84].

Throughout the life course, there are different hormone regulation pathways used by men and women that may be tied to cognitive health. Although not addressed during the think tank, the role of progesterone/progestins and the vehicle of delivery (concentrations) and

timing of delivery should also be considered. Whether such distinct hormonal disruptions for men versus women play a role in AD pathogenesis is unknown and is a significant gap in our understanding. Studies to investigate how hormonal changes may influence or impact the brain's ability to respond to injury in men and women in midlife and late life may give rise to greater understanding of biological underpinnings related to AD.

2.4. Metabolic and vascular factors' role in sex vulnerabilities

The metabolic syndrome, characterized by obesity, insulin resistance, hypertension, and dyslipidemia, has been linked to an increased risk of AD [85] and also increases during menopause [86]. Type 2 diabetes (T2D) has also been associated with an increased risk of AD [87,88]. Consistent with these human studies, profound cognitive impairments associated with reduced cerebral blood volumes are seen in female mice on a high-fat diet [89]. Although many of these factors may increase the risk for AD in both men and women, the risk factor may be stronger in one sex. As most studies have simply adjusted for sex, and not stratified by sex, more research is needed to determine what risk factors are most important in women and in men. Furthermore, sex-specific factors need to be considered. For example, additional metabolic contributors for women could include the decline in estrogen levels (as mentioned previously), increased adiposity, inflammation and neuroinflammation, and changes in glucose metabolism and insulin signaling [90].

Reduced cerebral glucose metabolism is one process that links insulin resistance to AD. Insulin resistance is also associated with cerebral hypometabolism in cognitively normal prediabetic older adults [91,92], greater brain amyloid deposition in the middle age [93], tau hyperphosphorylation, vascular dysfunction, inflammation, and dyslipidemia. The relationship between insulin and MCI or AD may also be moderated by sex and *APOE* ε4 genotype although the exact path or role for this interaction is unclear [94,95]. Both animal and human studies have suggested that the response to intranasal insulin supplementation differs by sex, with insulin slowing cognitive decline in women but not men [96], especially in noncarriers of the *APOE* ε4 allele [97], whereas *APOE* ε4 carriers do not respond well to insulin [97]. Furthermore, there was a worsened effect on cognition for the *APOE* ε4 carriers than noncarriers in this study [97]. A long-acting insulin analogue called insulin detemir has also been tested in adults with AD or MCI, showing significant effects on verbal working memory and visuospatial working memory when given at high doses [98].

Diabetes also appears to play a role in how women respond to hormone therapy. In the Women's Health Initiative (WHI), >27,000 postmenopausal women were randomly assigned to receive hormone therapy or placebo for an average of 5.6 years in women with intact uteruses and 7.2 years in those with prior hysterectomy, with follow-up for a total of 13 years [99]. In a substudy looking at the role of diabetes on brain volume, brain magnetic resonance imaging was done on 1402 participants 2.4 years after the trial and again on 699 participants 4.7 years later. This study showed that women with T2D who were assigned hormone therapy when 65 years or older were at substantial increased risk for lower brain volumes compared with those without diabetes [78] and suggests that estrogen therapy produced adverse cognitive effects in older women with diabetes. The same trend may also appear in men. A follow-up study in the WHI cohort suggested that hormone therapy

increased the risk of dementia in women with diabetes more than in women without diabetes [100]. Of note, this linkage to dementia could encompass vascular dementia as well as AD and related disorders. Among younger women, hormone therapy appears to be cognitive safe [100] so that the adverse interaction between hormone therapy and diabetes appears to occur only later in life [101].

Metabolic differences in women and men may also account for the differential response to other types of therapy. For example, women compared with men may experience greater benefit, as measured by both metabolism and cognition, from physical activity [102,103]. Studies that further investigate the contributing role of vascular and metabolic mechanisms to brain health for women compared with men may be important to think about in regards to designing and testing risk and intervention strategies for AD in both sexes.

3. Lifestyle factors

In addition to biological mechanisms, potentially modifiable lifestyle factors such as education, occupation, social activities, exercise, sedentary behavior, diet, sleep, and cultural factors appear to play important roles in predicting the risk of AD and may help explain both gender and geographical differences in risk of the disease. However, to date, the impact and the role of these particular risk factors are still under investigation. Factors that may contribute to disparities between US and European observations of dementia incidence include methodological differences, such as different sample sizes and diagnostic criteria, as well as cultural and historical events. For example, World War II and the Cold War affected stress levels, survival, educational attainment, and the environment differently in Europe compared with the United States [19]. Formal schooling for individuals earlier in life has significantly increased from a generation ago; for instance, in the United States, 53% of adults aged ≥65 years finished high school in 1990 compared with 80% in 2010. The impact of educational attainment between men and women may also be an area for investigation [19,20,104]. Men and women may experience and respond to stress in different ways. Sex differences have been demonstrated in the brain’s stress response circuitry, which includes multiple cortical and subcortical regions that regulate the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal axes [105,106]. The HPA axis responds to stress by secreting glucocorticoids—cortisol in humans—which has many varied physiological effects on metabolic, immune, cardiovascular, and cognitive processes. Dysregulation of the HPA axis is associated with many psychosomatic and psychiatric disorders [106] and with AD in humans and animal models [107]. In humans, HPA dysfunction and the increased risk of AD are reflected by increased levels of circulating cortisol [108]. More recently, the corticotrophin-releasing factor was shown to mediate the stress response and influence production of Aβ, which may help explain how stress may increase AD risk [109]. Sex hormones, both estradiol and androgens, have also been shown to modulate HPA axis responsiveness and the response to stress [110]. This, along with sexual dimorphism in the level of corticosteroid basal globulin, may contribute to the sex differences in stress response [106]. Whether sex differences in response to stress contribute to sex differences in AD risk has not been fully explored and requires further study. Interestingly, a role for *APOE* in the regulation of the stress response and metabolic alteration was identified in *APOE*-deficient

mice [111], and human *APOE* isoforms differentially affect measures of anxiety in human *APOE* mice and individuals with probable AD [111–113].

In both men and women, cognitive health may be especially vulnerable to certain kinds of stress—including adverse family events. For example, two European studies showed that economic recessions at the time of birth were associated with a negative effect on lifelong cognitive function in several domains [114,115]. The mechanisms underlying this finding are unclear but may relate to nutrition, disease exposure, educational level, and/or psychological stress. Interestingly, the existence of social networks appeared to improve cognitive function [114]. In studies that examine the link between stressful life events and risk for AD, women who experience sustained high stress compared with men have an increased likelihood of developing dementia [116]. In studies of anxiety as a risk factor for dementia, one prospective study found that if men and women were considered separately, anxiety was a significant risk factor for women but not for men [117]. As such, longitudinal studies assessing the long-term effects of stress on men and women are greatly needed to understand differential impact of both stress and also on stress-reducing interventions as potential tools to ameliorate symptoms. Such understanding may shed light on interventions, individually or in combination, that may be more beneficial for women and men.

Depression and sleep disorders may also promote cognitive decline differently in women compared with men. Women are two times more likely than men to be diagnosed with depression [118,119], and women who experience cumulative symptoms of depression over many years may have an increased risk for MCI and dementia in old age [120,121]. Studies comparing men and women do not consistently find gender differences in depression as a risk factor [122], although one report found depression greater than 10 years before dementia onset was a risk for dementia only in female *APOE* ε4 carriers and not in female noncarriers or in men [123]. Certain sleep disorders, such as insomnia and fragmented sleep, are also more prevalent in women than in men [124]. Change in sleep patterns can occur over the lifespan, often affecting women in different ways at different periods [125]. Studies have found links between various sleep disorders and changes in Aβ levels, glucose metabolism, and other processes that may be related to dementia onset and progression [126]. In addition, altered sleep may have especially profound effects on women with *APOE* ε4 and cardiovascular disorders, where problems with oxygenation in the brain may become more pronounced [127]. Largely uninvestigated is whether sleep problems are a greater risk factor for dementia in women than in men.

4. Moving forward

Participants in the workshop identified a number of areas where increased research is needed to better understand the role of sex and gender on AD risk. Although it is unclear if women are at increased risk, there are multiple lines of evidence to suggest that differential biological underpinnings may contribute to disease-related changes in women and men. Understanding these differences will be of key importance in developing strategies for intervention and diagnosis. These include

- Defining the role of sex chromosomes on AD-like biological changes, using GWAS and other techniques to more fully analyze the X and Y chromosomes.
- Determining how hormonal changes influence the brain and, specifically, cognition, including basic, translational, and clinical investigations.
- Examining the impact of *APOE* ε4 status impact on the pathophysiological pathways involved in AD dementia and AD pathology for women and how this may be similar or different for men.
- Investigating vascular and metabolic contributions to AD with specific focus on the biological pathways may contribute knowledge about how these factors may interact with sex to influence these pathways.
- Expanding the understanding of hormone-related changes in AD and dementia, including quantitative and longitudinal studies to explore life course exposure and changes.
- Exploring how sex differences in depression and altered sleep contribute to risk of cognitive decline, in pertinent animal models and utilizing big data approaches in human studies, such as the Global Alzheimer's Association Interactive Network, to understand how these disorders vary over the lifespan and how they may affect women differently from men.
- Quantifying the role and impact of risk and stressor contributors to risk for men and women, including but not limited to obesity, diabetes, etc.
- Understanding the role of stressors throughout life, including but not limited to child birth, hospitalizations, other comorbidities (i.e., cancer) on biologically relevant disease changes.
- Conducting clinical and epidemiologic studies that assess the effect of hormonal changes on AD-associated amyloid and neurodegeneration biomarkers from midlife to late life.
- Investigating sex-based therapeutic responses, including dose-response differences.
- Determining whether certain populations of women may benefit or suffer harm from hormone replacement as we probe further into personalized medicine for AD.

AD research involves more than scientific inquiry; it also requires political and financial support from society at large. To promote these goals, a group of philanthropic partners and advocates joined the gender vulnerability think tank discussion to further underscore that a greater understanding of AD—and the costs it presents to society—could make the study and eradication of AD a more urgent public concern. Mobilizing women and communities to promote funding for sex-related differences in AD is essential. There is a significant call to action for the Alzheimer's Association to identify and fund meritorious projects that further advance our understanding of sex-related differences in AD. Such investigations will

illuminate the fundamental biological underpinnings of AD and inform future therapeutic development for men and women affected by this disease.

5. Conclusions

Women experience a greater AD burden than men, both as individuals who develop the disease and as caregivers. During a 2-day discussion, the Alzheimer's Association think tank on biological sex- and gender-related vulnerabilities examined a wide variety of biological pathways and lifestyle factors that might be linked to this increased burden. It also raised several important questions: Why are women with *APOE* ε4 more likely to have severe AD? Which X-chromosome genes may influence resilience or vulnerability to AD in women? Is there a specific population of women who may benefit from estrogen therapy? Could selective estrogen and androgen receptor modulators be treatment options? How may earlier treatment of anxiety, depression, sleep disturbance, or metabolic disease help prevent or delay dementia in women?

All these questions suggest numerous avenues for future AD studies. Basic science research at the molecular level will need to focus on how age-related changes in estrogen and androgen receptor function, loss of telomere length, metabolic alterations, and other processes of aging are related to cognitive decline. Clinical studies will need to explore how hormones interact with changes linked to pre-clinical AD, including inflammation and toxic AP and tau clumping. Since this meeting, the Alzheimer's Association launched the *Sex and Gender in Alzheimer's Disease* request for applications through the Association's International Research Grant Program to fund scientific investigations addressing essential questions generated during the think tank and to move to a greater understanding of the underlying pathophysiology of AD.

Ultimately, the most effective dementia therapies may need to be tailored for each individual, taking into account factors tied to genetics, metabolic state, bioenergetics, lifestyle, comorbidities, and stage of life. This tailored approach has already shown promise in the treatment of cancer and other diseases once thought to be incurable, but which are now eminently treatable and do not prevent afflicted individuals from enjoying long, productive lives. By working together, the scientific community along with stakeholders across the board will achieve a world where AD cannot limit our ability to live long, vigorous, vital lives; understanding how sex differences contribute to AD risk may provide important clues to achieving this goal.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: Women experience a greater AD burden than men, both as individuals who develop the disease and as caregivers. The Alzheimer's Association convened an expert think tank to focus on the state of the science and level of evidence around gender and biological sex differences for AD.
2. Interpretation: During this 2-day think tank, researchers focused on knowledge gaps and areas of science that need to be more fully addressed. Discussion focused on biological sex- and gender-related vulnerabilities and examined a wide variety of mechanistic pathways and lifestyle factors that might be associated with this increased burden. Participants in the think tank identified a number of areas where increased research is needed to better understand the role of sex and gender on AD risk.
3. Future directions: By working together, the scientific community along with stakeholders across the board will achieve a world where AD cannot limit our ability to live long, vigorous, vital lives; understanding how sex differences contribute to AD risk may provide important clues to achieving this goal.