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Review Article

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 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

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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