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## Sex and Gender Differences in Alzheimer’s Disease Dementia

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### Introduction

Alzheimer’s disease (AD) dementia is the most common form of dementia, comprising 60 to 70 percent of all cases. AD is a progressive neurodegenerative disease that causes memory loss, cognitive deficits, and behavioral changes. The hallmark characteristics of AD include the presence of extracellular amyloid-beta plaques, intracellular neurofibrillary tangles, and neurodegeneration. With the aging of the population, the burden of AD dementia is growing to epidemic proportions. More than five million people in the United States currently have a diagnosis, and it is estimated that 14-16 million will be diagnosed with the disease by 2050 unless new treatments or interventions to prevent or delay the onset of AD are identified.<sup>1</sup> A declining trend in the risk of dementia has been reported for several high income countries in the past 20 to 30 years. However, the impact of these trends on the future remains uncertain and it is not clear what type of dementia may be driving these trends.<sup>2</sup>

Precision medicine techniques and approaches have emerged over the last decade and have advanced our understanding of the pathophysiological changes associated with the development and progression of AD dementia. However, the examination of sex and gender differences has not been well integrated into these approaches.<sup>3</sup> This is surprising given the extensive literature demonstrating sex differences in brain structure and function over the lifespan. There are also several misconceptions about the study of sex and gender in the AD field.<sup>4,5</sup> In this brief overview, the initial focus is on the question, “Are women at greater risk?”. A few examples of risk factors for AD that differ by sex are then provided, followed by an overview of potential differences in comorbid neuropsychiatric symptoms. Throughout, we utilize the Institute of Medicine definitions of sex and gender.<sup>6</sup> Sex refers to the biological and physiological differences between women and men, with the sex chromosomes (X and Y) contributing to these differences. Gender refers to a combination of environmental, social, and cultural influences on women and men. Gender is rooted in biology but it is primarily shaped by environment and experience.

### Are Women at Greater Risk?

Historically, the primary reason stated for examining sex or gender differences in AD dementia is that ‘women are at greater risk’ and that there is a need to understand what factors contribute to the greater risk for women. However, this rationale needs to be

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reassessed. About two thirds of persons diagnosed with AD dementia are women.<sup>1</sup> However, the life expectancy for women is longer than for men, and age is the greatest risk factor for AD dementia. As a result, and similar to other aging-related diseases, the lifetime risk of AD dementia is greater for women.<sup>7</sup> Although the frequency, or count, of AD dementia is higher in women, sex differences in the incidence of AD dementia are less clear, and may vary across countries and over time epochs.<sup>2</sup>

Incidence is defined as the total number of individuals developing a disease in a given time period divided by the number of people at risk of the disease. For example, we would like to know whether the risk (incidence) of developing AD dementia over the next three years differs for women versus men who are 85 years old and do not have a diagnosis of dementia. In the United States, studies overwhelmingly report that the incidence of AD dementia does not differ by sex, even after the age of 85 years.<sup>e.g.8</sup> In other areas of the world, women do appear to have a higher incidence. For example, studies in several European countries report that women have a higher incidence of AD dementia after the age of 80.<sup>e.g.9,10</sup> However, the Cognitive Function and Aging Study in the United Kingdom initially reported a higher incidence for men.<sup>11</sup> The reasons for these discrepancies are not well understood, but suggest that sex and gender differences in the incidence of AD dementia may depend on the time period and geographical region.<sup>4</sup> For example, the experiences of World Wars I and II were vastly different in European countries compared to those in the United States and in men compared to women.<sup>2</sup> The study of these world-wide differences is needed and provides an opportunity to identify modifiable risk factors for AD dementia. Notably, these studies also highlight the fact that AD is not a disease unique to women, but that many men are also affected.

### Sex and Gender Differences in Risk Factors for AD Dementia

Even if women and men have the same incidence of AD dementia (age- and sex-specific incidence rate), the mechanisms, pathways, and risk factors can still differ. Many studies examining risk factors for AD ‘adjust’ for sex in the analyses, but they do not determine whether there are actual sex differences (i.e., whether the strength of the association between a risk factor and AD dementia differs by sex). There are multiple scenarios by which sex and gender differences could affect the risk of AD dementia: 1) Risk factors with the same frequency for women and men but that have a stronger effect in one sex or another (e.g., *APOE* genotype or other genetic variants located on autosomal chromosomes); 2) Risk factors that have the same effect in women and men but that have a different frequency (e.g., historically, women have had less access to education and men have a higher frequency of smoking); 3) Risk factors that both differ by sex in frequency and effects (e.g., head trauma is more common in men compared to women, but women may be more susceptible to the adverse effects from the head injury); and 4) Risk factors restricted to one sex (e.g., pregnancy, oophorectomy; prostate cancer and androgen deprivation therapy).<sup>5</sup> Herein, we provide a brief description of some risk factors that fit these scenarios.

**Examples of sex differences in risk factors—**Women have twice the risk of depression compared to men.<sup>12</sup> Depression has implications for cognition across the lifespan because mood and memory map to some of the same brain regions. Studies report that

depression is a risk factor for AD dementia in both women and men,<sup>e.g., 13</sup> with estimates as high as a 70% increased risk of AD dementia for those with depression in midlife.<sup>14</sup> Therefore, because the life-long prevalence of depression is greater in women, a diagnosis of depression may have a greater overall impact for AD dementia risk among women.

In contrast to depression, men have a greater overall prevalence of sleep apnea, although the prevalence of sleep apnea in women significantly increases after menopause.<sup>15</sup> Sleep apnea and poor sleep quality have been associated with cognitive decline and an increased risk of AD dementia.<sup>e.g.16</sup> Given that men have a higher prevalence of sleep apnea, the effect of this risk factor may have a greater overall impact in men. Notably, there is a lack of studies examining whether the association between sleep apnea and AD dementia differs by sex.

**Examples of gender differences in risk factors**—Low education has consistently been associated with an increased risk of AD dementia for both women and men.<sup>17</sup> However, in the past century, women have had fewer opportunities for higher education (lower frequency); therefore, the risk of AD dementia attributable to low education is greater for women. One study also suggested that lower education may have a stronger deleterious effect for AD dementia in women, independent of their access to education.<sup>18</sup> More recently, educational attainment for women has been higher than men in the United States. The progressive improvement in education in women over the last century may be one explanation as to why the incidence of dementia may be declining more for women than men in some countries.<sup>19</sup>

Men who have never married or are widowed, have a greater risk of developing AD dementia compared to women.<sup>20</sup> A possible reason is that women have historically been responsible for the healthcare of their family (e.g., getting partners/husbands to healthcare providers for regular check-ups, assuring everyone has a healthy diet, etc.), sometimes at the expense of their own health. Single women, compared to single men, are also more likely to see a healthcare provider and to engage in social activities, which are beneficial for cognition. Although these observations are a bit stereotypical and not true in all situations, they may explain part of the difference in risk. Caregivers of older, single, or widowed men should be cognizant of this increased risk, and in turn help to maintain regular check-ups and engagement in some type of social activity.

**Examples of sex-specific risk factors**—Pregnancy and menopause are specific to women. Hypertensive pregnancy disorders (HPD) affect approximately 12% of all pregnancies. A history of HPD has been associated with an increased risk of brain atrophy and cognitive decline decades after the pregnancy.<sup>21</sup> However, the association between HPD and specific types of HPD and the risk of AD dementia has not yet been examined. Menopause is a universal event for women who live to midlife. The menopausal transition has been associated with a decrease in verbal memory,<sup>22</sup> and early menopause (e.g., either natural or surgically) has been associated with an increased risk of dementia.<sup>e.g.23</sup> In particular, premenopausal bilateral oophorectomy resulting in the abrupt loss of ovarian hormones has been associated with both an increased risk of dementia and of accelerated aging.<sup>e.g.23</sup>

There is still much debate regarding the use of estrogen-containing hormone therapies and type (e.g., conjugated equine estrogens versus 17 $\beta$ -estradiol patch) for mitigating the risk of AD dementia in women. Although initial results from the Women's Health Initiative Memory Study suggested that women who were randomized to start taking estrogen therapy after the age of 65 years were at greater risk of dementia,<sup>24</sup> recent clinical trials and observational studies have not found an association (either negative or positive) with cognitive decline or dementia risk when hormone therapy is initiated within 5 years of menopause. e.g.<sup>25</sup> These more recent studies indicate that it is safe to treat menopausal symptoms (including hot flashes or sleep and mood changes) without the concern for an increased risk of dementia. However, additional research is clearly needed.

Prostate cancer is unique to men. Androgen-deprivation therapy (ADT) is now used for more than one-half of all men with prostate cancer at some stage after diagnosis.<sup>26</sup> Some studies, e.g.<sup>27</sup> but not others, e.g.<sup>28</sup> suggest that ADT is associated with cognitive decline and risk of dementia. Additional studies are needed to determine the long-term effects of ADT for risk of dementia in men.

### Psychiatric Symptoms of AD Dementia

Most AD dementia patients experience neuropsychiatric symptoms (NPS) at some point during the course of the disease.<sup>29</sup> These symptoms lead to poorer medical and functional outcomes as well as increased caregiver burden. Recent studies suggest that the distribution of NPS may vary by sex. In a study of newly diagnosed AD dementia patients who were not treated for AD or NPS, women had a higher mean NeuroPsychiatric Inventory (NPI) score for depression, anxiety, and for total NPS.<sup>30</sup> Several other studies have also found higher depressive symptoms in women with a diagnosis of AD dementia compared to men. e.g.<sup>31</sup> In contrast, men with AD dementia are more likely to have agitation compared to women. e.g.<sup>31</sup> Better characterization of the sex differences in NPS among AD dementia patients will help to elucidate sex differences in the disease pathophysiology and to identify better treatment targets for both women and men.

### Conclusion

The study of sex and gender differences in the AD field is in its infancy compared to other areas of medicine such as cardiology. The field of cardiology has shown that there are sex and gender differences in risk factors, symptom presentation, mortality, and treatment response for cardiovascular diseases. Better understanding of these sex and gender differences has led to improved care and treatment for both women and men. The same positive outcome can occur for the prevention and treatment of AD dementia. We must move beyond the notion that "women are at greatest risk" and that AD dementia is a "women's disease" to focus on sex and gender differences. This brief overview provided a few scenarios of sex and gender differences in risk factors for, and clinical presentation of, AD dementia. There will not be sex or gender differences in all risk factors or mechanisms. However, identifying where there are differences will provide better treatment and care for both women and men.

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