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Featured Article

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

Rebecca A. Nebel[a,*], Neelum T. Aggarwal[b], Lisa L. Barnes[b], Aimee Gallagher[a], Jill M. Goldstein[c,d], Kejal Kantarci[e], Monica P. Mallampalli[a], Elizabeth C. Mormino[f], Laura Scott[g], Wai Haung Yu[h], Pauline M. Maki[i,j,1], Michelle M. Mielke[k,l,1]

[a]*Scientific Programs, Society for Women's Health Research (SWHR®), Washington, DC, USA*
[b]*Department of Neurological Sciences and the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA*
[c]*Department of Psychiatry, Harvard Medical School, and Massachusetts General Hospital, Boston, MA, USA*
[d]*Department of Medicine, Harvard Medical School, and Massachusetts General Hospital, Boston, MA, USA*
[e]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[f]*Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA*
[g]*Cellular and Molecular Medicine Program, Johns Hopkins University, Baltimore, MD, USA*
[h]*Department of Pathology and Cell Biology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA*
[i]*Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA*
[j]*Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA*
[k]*Department of Epidemiology, Mayo Clinic, Rochester, MN, USA*
[l]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

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.

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

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[1]Co-senior authors

*Corresponding author. Tel.: 202-496-5002; Fax: 202-833-3472.
E-mail address: rebecca@shwr.org

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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 in women and the eighth leading cause of death in 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-β (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 has 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 and gender 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

Table 1
Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease members and their affiliations

Pauline M. Maki, PhD, Network Chair, Professor, Psychology and Psychiatry, University of Illinois at Chicago
Michelle M. Mielke, PhD, Network Co-Chair, Professor, Health Sciences Research, Division of Epidemiology, and Professor of Neurology, Mayo Clinic
Neelum T. Aggarwal, MD, Associate Professor, Neurological Sciences, Rush University Medical Center
Lisa L. Barnes, PhD, Professor Behavioral Sciences, Neurological Sciences, Rush University Medical Center
Jill M. Goldstein, PhD, Professor, Psychiatry and Medicine, Harvard Medical School and Massachusetts General Hospital
Kejal Kantarci, MD, MS, Professor, Radiology, Mayo Clinic
Elizabeth C. Mormino, PhD, Assistant Professor, Neurology & Neurological Sciences, Stanford University
Wai Haung Yu, PhD, Assistant Professor, Pathology & Cell Biology, Columbia University