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August 20, 2020

Submitted electronically to:

<https://www.surveymonkey.com/r/QLDVJY6>

Submitted via email to: DementiaCareSummit2020@nih.gov

Richard J. Hodes, MD
Director, National Institute on Aging
Room 5C35, Building 31
9000 Rockville Pike
Bethesda, MD 20892-2292

Jennifer L. Wolff, PhD
Professor, Johns Hopkins University
Co-Chair, 2020 Summit Steering Committee
624 N. Broadway, Hampton House 692
Baltimore, Maryland 21205

David Reuben, MD
Director of Geriatric Medicine, UCLA
Co-Chair, 2020 Summit Steering Committee
10945 Le Conte Avenue, Suite 2339
Los Angeles, CA 90095

Re: NOT-AG-20-035 Request for Information: Invitation for Input on Research Gaps and Opportunities related to the 2020 National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers

Dear Dr. Hodes, Dr. Wolff, Dr. Reuben, and members of the National Institute on Aging (NIA) 2020 Dementia Care, Caregiving, and Services Research Summit Steering Committee,

The Society for Women's Health Research (SWHR) is pleased to offer feedback on the committee's draft of the research gaps and opportunities discussed during the summit's virtual meeting series. SWHR appreciates the opportunity to provide specific comments, as directed in NIA's June 26, 2020, Request for Information (NOT-AG-20-035).

SWHR is a 30-year-old national nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. In 2016, SWHR launched an interdisciplinary

network¹ of eight top Alzheimer's researchers and clinicians to examine sex-based differences in Alzheimer's disease (AD). For the past four years, the network has worked to better understand and leverage the roles of sex and gender in AD to inform prevention and treatment and provide guidance for research, clinical trials, and policy. The network has published in peer-reviewed scientific journals² as well as more popular media outlets such as STAT³ and Scientific American.⁴

When identifying gaps and opportunities in AD and Alzheimer's disease-related dementia (ADRD) research, it is crucial to acknowledge the impact that AD has on women. Of the 5.8 million American adults diagnosed with AD, about two-thirds are women. While AD is the 7th leading cause of death for men, it is the 5th leading cause of death for women.⁵ Our ability to devise new strategies for prevention and treatment is impeded by a lack of knowledge about how and why the disease differs between women and men.

We have some evidence, for example, that sex hormones such as estrogen influence the course of the disease, but we do not understand enough about why and how. In addition, the $\epsilon 4$ allele of the *APOE* gene is the most common genetic risk factor for AD in both women and men, but women with $\epsilon 4$ allele are at greater risk for developing AD than men with the $\epsilon 4$ allele — though we don't know why.⁶

Unfortunately, in reviewing relevant research, most studies of AD and ADRD risk combine data for women and men. Scientists have often overlooked sex and gender differences in diagnosis, clinical trial design, treatment outcomes, and caregiving, hindering progress in detection and care. Approaches that incorporate sex and gender differences into research have advanced innovation in many other diseases. We need to do the same for Alzheimer's.

SWHR commends NIA for compiling a thorough list of research gaps and opportunities. We applaud the steering committee for emphasizing the fact that health disparities affect all six of the included themes, from long-term care to evaluation and treatment. With this being said, SWHR is disappointed to see that the topic of disparities is not given its own theme, despite the significant gaps and opportunities for advancement in this area.

SWHR strongly urges the steering committee to consider broadening the scope to discuss disparities in dementia with increased specificity that will better drive research in this area. We believe AD/ADRD needs in regards to disparities are extensive enough to create a theme focused solely on this topic. Alternatively, we strongly recommend that disparities related to sex, gender, race, ethnicity, and other demographic factors be highlighted with greater depth and specificity across themes.

¹ SWHR (2016). Society for Women's Health Research launches new interdisciplinary network to focus on sex differences in Alzheimer's disease. Retrieved from: <https://swhr.org/society-for-womens-health-research-launches-new-interdisciplinary-network-to-focus-on-sex-differences-in-alzheimers-disease/>

² Nebel, RA., et al. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's Dement.*, 14(9): 1171–1183. doi: 10.1016/j.jalz.2018.04.008

³ Miller, A. & Nebel, R. (2018). Studying sex differences will improve health for women and men. *Stat.* Retrieved from: <https://www.statnews.com/2018/06/13/studying-sex-differences-women-men/>

⁴ Nebel, R. (2018). Alzheimer's hits men and women differently, and we need to understand why. *Scientific American.* Retrieved from: <https://www.scientificamerican.com/article/alzheimers-hits-men-and-women-differently-and-weneed-to-understand-why/>

⁵ <https://www.cdc.gov/nchs/fastats/alzheimers.htm>

⁶ Ibid.

In regards to sex and gender specifically, NIA's draft gaps and opportunities address gender issues within theme one (impact of dementia) only. Sex and gender are thereafter not incorporated within any of the remaining topics. Moreover, the role of sex as a biological variable (SABV) and the obvious research gaps presented by inadequate use of SABV within outcomes analyses is not addressed at all. We hope NIA will consider a more thorough incorporation of both sex and gender issues within the finalized review of opportunities.

In a 2018 paper published by SWHR's AD network in the peer-reviewed *Alzheimer's & Dementia* journal,⁷ SWHR defined 12 priority areas for attention in future research. We review these priority areas below. We recommend these areas be specifically highlighted as gaps and opportunities within AD and ADRD research:

1. *The extent to which findings of sex and gender differences in AD are due to differences in longevity, survival bias, and comorbidities.* We know that age is the major risk factor for AD, that women live longer than men, and that more women than men will develop AD over their lifetime. We need to understand more about biological and sociocultural differences between women and men that may influence longevity and survival bias.
2. *Potential sex-specific risk factors for AD (e.g., oophorectomy, menopause, pregnancy, androgen-deprivation therapy, and testosterone loss) across the lifespan.* Early surgical removal of the ovaries is associated with cognitive decline, and hypertensive pregnancy disorders (HPDs) are associated with increased risk of brain atrophy later in life. Research must seek to understand the increased AD risk in women with early surgical menopause, and whether common underlying factors increase the risk of both HPDs and AD, or whether HPDs are an independent risk factor for AD.
3. *The influence of estrogens and hormone therapy on brain function and AD risk in light of discrepancies in the clinical literature.* There is evidence that the transition into menopause affects certain aspects of memory and that hormone therapy (HT) has a neutral effect on cognition in early post-menopause — but findings on HT and dementia are mixed. We need to better understand how HT influences cognition and AD risk, the cause of the discrepancies in current findings, and how HT influences AD biomarkers.
4. *Potential sex differences in genetic risk factors for AD.* The $\epsilon 4$ allele of the *APOE* gene is the strongest genetic risk factor for late-onset AD. Women with *APOE* $\epsilon 4$ have an increased risk of developing AD compared to women without *APOE* $\epsilon 4$ and men both with and without *APOE* $\epsilon 4$. Research should attempt to discover the mechanisms underlying the interaction between sex and *APOE* for AD risk, as well as whether other genetic AD risk factors are stronger for women than men or vice versa and whether genes on the X or Y chromosomes affect AD risk.
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.* There are a variety of AD risk factors that differentially affect women and men, and we must seek to understand how the development of these risk factors affect women and men, and which modifiable risk factors are strongest for the development of AD in each sex.

⁷ Nebel, RA., et al. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's Dement.*, 14(9): 1171–1183. doi: 10.1016/j.jalz.2018.04.008

6. *Sex differences in AD progression and the trajectory of change in cognitive function, neuroimaging, and biomarkers of AD.* Women with mild cognitive impairment (MCI) show greater brain atrophy and cognitive and clinical decline than men. Women with the same amount of AD pathology as men also show more severe clinical symptoms of AD. We need to assess why women may be more vulnerable to AD pathology.
7. *The effects of sex differences in brain development on sex differences in brain aging and, ultimately, AD pathology and dementia.* The female vulnerability for major depressive disorder and cardiovascular disease — both risk factors for AD — begins in fetal development. Sex steroid hormones have organizational effects on the brain that contribute to sex differences in cognition. Research should attempt to address how sex differences in brain development ultimately contribute to 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.* African Americans and Hispanic/Latinos are 1.5 to 2 times more likely to be diagnosed with AD or related dementias than European Americans. Minority populations are underrepresented in AD research, including clinical trials and biomarker studies. More work should be done to determine whether the increased AD risk is uniform across both sexes in minority populations, and whether there are sex and gender differences in risk factors, disease progression, or biomarkers in minority populations.
9. *The factors involved in the secular changes (e.g., societal, political) and geographical variation in estimates of sex differences in AD.* In some regions/countries, women appear to be at greater risk of AD at older ages. The experiences of women and men in wars and political conflicts have historically differed both within and across countries. In the past century, women have also had fewer educational and job opportunities. Therefore, we must attempt to understand whether historical experiences of women and men differentially impact AD risk (e.g., effects of stress, famine) and whether low socioeconomic status and job attainment pose similar AD risk for women and men.
10. *Gender differences in caregiving and how the burden of caregiving influences AD risk.* Women make up about 60% of family caregivers, and rates are even higher for Hispanics and African Americans. Female caregivers report a twofold higher level of caregiver burden compared to male caregivers, and caregiving is associated with elevated levels of cortisol and impaired attention and executive function. Studies should investigate how gender differences in caregiver responsibilities may impact AD risk.
11. *Sex and gender differences in developing AD therapeutics, from preclinical to clinical studies, and in the design of clinical trials.* The 1993 NIH Revitalization Act required that women be included in all NIH-funded studies and that trials be designed to permit analysis of different effects. In 2016, NIH began requiring researchers to factor sex as a biological variable into the design, analyses, and reporting of preclinical studies. Although analyses of clinical trial data generally include sex as a variable, equivocal treatment effects may not be reported, making it difficult to compare this information.

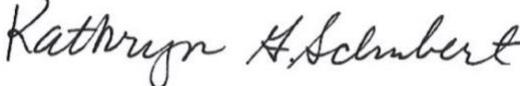
12. *The effects of sex and gender differences on the clinical detection, diagnosis, management, and treatment of AD.* The diagnosis of MCI and AD relies on tests of verbal memory (e.g., memory for word lists, stories). There is a lifelong female advantage in verbal memory. Among those with MCI, women perform better than men on tests of verbal memory despite having the same level of AD-related pathology. Research should address whether the female advantage in verbal memory delays diagnosis for women, possibly limiting opportunity for early intervention. We also must address whether the use of sex-specific cutoff scores to detect impairment in verbal memory tests would improve diagnostic accuracy.

Assessing sex and gender differences in AD represents an opportunity to improve clinical detection, diagnosis, management, and treatment of AD for both sexes. We are hopeful that future research and policy proposals will consider these historically overlooked key areas.

Thank you for your leadership in advancing Alzheimer's research and care in the United States. We look forward to seeing the finalized 2020 Summit research gaps and opportunities pertaining to Alzheimer's disease.

If you have any questions, please feel free to contact our Director of Science Policy and head of the SWHR Interdisciplinary Network on Alzheimer's Disease, Melissa Laitner, PhD, MPH, at melissa@swhr.org.

Sincerely,



Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research