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March 13, 2020

The Honorable Patrick J. Toomey
Chairman
Senate Finance Committee Subcommittee on Health Care
248 Russell Senate Office Building
Washington, DC 20510

The Honorable Debbie Stabenow
Ranking Member
Senate Finance Committee Subcommittee on Health Care
419 Hart Senate Office Building
Washington, DC 20510

Dear Chairman Toomey and Ranking Member Stabenow,

The Society for Women's Health Research (SWHR) is pleased to respond to the request of the Senate Finance Committee and the Health Subcommittee for feedback on actions to address Alzheimer's disease (AD). 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. Age is the strongest risk factor for AD, and women live longer than men, but longevity alone does not wholly explain the higher frequency and lifetime risk in women or the differences seen between women and men in AD risk, presentation, and progression.

In 2016, SWHR launched an interdisciplinary network of eight top Alzheimer's researchers and clinicians to examine sex-based differences in AD. For the past four years, the network has been actively working to understand and leverage the scientific basis of 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 the results of its efforts in peer-reviewed scientific journals¹ as well as more popular media outlets such as STAT² and Scientific American.³

¹ As-Sanie, S., Black, R., Giudice, L., Valbrun, T., Gupta, J., Jones, B., Laufer, M., Milspaw, A., Missmer, S., Norman, A., Taylor, R., Wallace, K., Williams, Z., Yong, P., Nebel, R. (2019). Assessing Research Gaps and Unmet Needs in Endometriosis American Journal of Obstetrics and Gynecology 221(2), 86-94. <https://dx.doi.org/10.1016/j.ajog.2019.02.033>

² 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/>

³ 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-we-need-to-understand-why/>

Based on the extensive work of our AD network, SWHR has recommendations for encouraging research and innovation within this field. Our feedback aligns predominantly with the requested areas of input focused on Improving Detection and Care and Encouraging Innovation.

Prioritize AD Research That Addresses Sex- and Gender-Specific Risks

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.⁴ Our ability to devise new strategies for AD 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, Apolipoprotein E4 (apoE4), the most common genetic risk factor for AD, is expressed in more than half of AD patients and is a new area of focus for many scientific researchers targeting potential therapies. However, women with the allele are at greater risk for developing AD than men with the allele — though we don't yet know why.⁵

Unfortunately, in reviewing relevant research, most studies of AD risk combine data for women and men. Scientists have often overlooked sex 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 other diseases. We can – and must – do the same for Alzheimer's.

In a 2018 paper published by SWHR's AD network in the peer-reviewed *Alzheimer's & Dementia* journal, we defined 12 priority areas for attention in future research in the following categories. Specifically, we recommend that research-related policy engage and invest in the following key areas:

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

⁴ National Center for Health Statistics (2016). Alzheimer's disease. Retrieved from: <https://www.cdc.gov/nchs/fastats/alzheimers.htm>

⁵ Safieh, M., Korczyn, A.D., & Michaelson, D.M. (2019). ApoE4: An emerging therapeutic target for Alzheimer's disease. *BMC Medicine*, 17 (64). doi: 10.1186/s12916-019-1299-4

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.
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.

Caregiving is associated with elevated levels of cortisol and impaired attention and executive function. Dementia caregivers are broadly at risk for a variety of health difficulties, including increased rates of chronic conditions, more frequent interactions with the health care system, decreased engagement in healthy preventative behaviors, and increased behavioral health concerns, such as smoking. Caregivers also demonstrate poorer immune responses to vaccines, slowed healing time, and reduced overall immunity to diseases.⁶

Caregiving has a broader economic impact as well. When faced with the need to forego employment to attend to a family member that requires full-time assistance, caregivers face hardships including loss of earnings and employee benefits, loss of social service benefits, and inability to contribute to a retirement fund or participate in a pension plan. Individuals facing financial restraints may be significantly less likely to attend to preventative health care behaviors or regular appointments, or may face challenging out-of-pocket costs for their own health care or for their family's care. This in turn creates increased financial burden to our national health care system. Given that women make up the majority of caregivers, this population is disproportionately impacted by economic and financial concerns.

It has been hypothesized that spousal caregivers may be at higher risk of cognitive impairment or dementia than noncaregiver spouses in response to several psychosocial (e.g., depression, social isolation, and sleep problems), behavioral (e.g., exercise and diet), and physiological (e.g., metabolic syndrome and inflammation) variables. 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.

⁶ Brodaty, H., & Donkin, M. (2009). Family caregivers of people with dementia. *Dialogues of Clinical Neuroscience*, 11(2), 217-28.

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.

Estimate of Cost or Savings to the Federal Government

SWHR does not see a need for additional investment at this time should current funding be allocated in a way that is supportive of the research priorities listed here. However, we would be happy to make recommendations for appropriate investment amounts, should the federal government deem additional investment necessary to address these areas of research need. SWHR is supportive of continued robust funding for the National Institutes of Health.

Thank you for your leadership in advancing Alzheimer's research and care in the United States. We look forward to seeing future Senate Finance Committee legislation 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 or 202-496-5002.

Sincerely,



Amy M. Miller, PhD
President and Chief Executive Officer
Society for Women's Health Research