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Experts Respond to Article on Sex-driven Modifiers of Alzheimer Risk

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Many of you may have seen the recent published-ahead-of-print article, “Sex-driven modifiers of Alzheimer risk: a multimodality brain imaging study,” by Aneela Rahman and colleagues in *Neurology,* in which the findings suggest that there may be an opportunity for intervention in early menopause for Alzheimer disease in women. This is an important issue for healthcare providers in their care of midlife women.

It is important that we have experts on the topic to provide commentary on the significance of these findings, so I invited my esteemed colleagues and experts in the field, Dr. Kejal Kentarci and Dr. Pauline Maki, to provide guidance for us. I’m pleased to share their wisdom, and I thank them for their commentary.

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Rahman and associates describe findings from a cross-sectional investigation of sex differences in neuroimaging biomarkers associated with late-onset Alzheimer disease (AD). The sample was relatively small, comprised of 85 women and 36 men ranging in age from 40 to 65 years. Biomarkers of AD pathology included amyloid beta (Aβ) ligand uptake via 11C-Pittsburgh compound B [PiB] PET and biomarkers of neurodegeneration such as decreased glucose metabolism on F-18 fluorodeoxyglucose (FDG) PET and reduced gray and white matter volumes. Of interest to NAMS members, postmenopause status and hysterectomy were associated with increased AD biomarkers, whereas hormone therapy (HT) was associated with decreased risk. Indeed, these factors were more strongly associated with AD risk than the more established clinical, medical, genetic, and lifestyle factors.

There is considerable merit in investigating sex differences in AD biomarkers and the role of menopause-related factors in AD risk. However, the rather small sample size (36 men; ~42 postmenopausal women; 8 women with hysterectomy, ~14 HT users), the high prevalence of *APOE* ε4 genotype (42% of women), the strongest genetic risk factor for late-onset AD dementia, and family history of AD (79% of sample) raise questions about the reproducibility and generalizability of findings to the broader population.

A high proportion of *APOE* ε4 carriers in the study sample may have influenced the findings, particularly during menopause when the risk of Aβ accumulation first begins to increase in *APOE* ε4-positive women. Other studies show the important modulating effects of *APOE* ε4 on AD biomarker abnormalities in women compared with men, although the sample size in the current study was too small to examine such effects. For example, in 5,400 clinically normal participants, women who were *APOE* ε4 carriers had an elevated risk of clinical progression to AD compared with *APOE* ε4 men and *APOE* ε4-negative women. In other work, female *APOE* ε4 carriers appear to show earlier cognitive decline and AD biomarker positivity compared with other groups.

Some findings were at odds with the broader literature. First, there was no single neuroimaging outcome in which men showed worse outcomes than women. In larger longitudinal investigations such as the Baltimore Longitudinal Study of Aging, men show steeper declines in brain volume as early as the sixth decade. Second, menopause-related factors were more strongly related to the AD biomarkers than the more established markers of AD risk in the field, including the *APOE* ε4. Larger longitudinal studies have not shown consistent evidence that HT positively influences AD biomarkers.

Although the focus of the current study was on AD biomarkers, neurofibrillary tangle (NFT)-tau biomarkers, the second hallmark of AD (besides amyloid-β), was not assessed. There is evidence that early NFT-tau deposition is higher in women than in men and that women are more clinically affected by the combined influence of tau and amyloid-β early in the disease.

It is also important to consider the broader implications of this work. All women who live into late life transition through the menopause, but most women will live their lives free of AD. Further, although two-thirds of patients with AD are women, there appears to be no sex difference in the incidence of AD once longevity is taken into account. Understanding which women may be at risk for AD because of menopause-related factors is an important goal, and this study appears to reinforce the idea that *APOE* ε4 carriers may be among those factors.

Rahman A, Schelbaum E, Hoffman K, et al, Sex-driven modifiers of Alzheimer risk: a multimodality brain imaging study [published online ahead of print June 24, 2020]. *Neurology*.