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Apolipoprotein E ε4 and Risk Factors for Alzheimer Disease—Let’s Talk About Sex

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The apolipoprotein E ε4 (APOE4) allele is the most potent genetic risk factor for late-onset Alzheimer disease (AD) and female sex is associated with increased risk. In both sexes, carriers of the APOE4 allele harbor a dose-dependent increase in risk of AD development, compared with those with the neutral APOE3 or protective APOE2. We understand the APOE4 risk to be greater in women, and our current dogma raises several questions. Is female vulnerability to APOE4 a robust association in AD? If so, what mechanisms underlie the sex difference? Most importantly, is this sex difference of real consequence to human health?

Apolipoprotein E (APOE) is a polymorphic glycoprotein with myriad effects throughout the lifetime and within several disease states. It is particularly ubiquitous in the brain, where it regulates lipid and neuronal homeostasis. The 3 common human isoforms of APOE, ε2, ε3, and ε4, arise from a single locus on chromosome 19 and differ only in 2 discrete amino acid sequences (residues I12 and I58). Yet, this minute difference confers major consequences on molecular and physiological functions in the pathogenesis of AD.

Apolipoprotein E modifies Aβ-dependent and Aβ-independent mechanisms. The isoforms differentially regulate amyloid-β precursor protein transcription and Aβ production and secretion; APOE ε4 exerts the most potent effect and APOE ε2 the least. This could explain, in part, why APOE ε4 is deleterious. Similarly, the APOE isoforms differentially modify Aβ aggregation and clearance. In addition to Aβ-dependent effects, strong evidence supports Aβ-independent roles for APOE ε4 in the pathogenesis of AD including fragment toxicity, tau phosphorylation, synapatic vulnerability, and impairment of mitochondrial function.

Are women more vulnerable to deleterious effects of APOE ε4? In large-scale clinical and preclinical studies of risk, disease course and biomarkers, APOE4 carriers (ε3/ε4) were more likely to develop AD, an effect that was amplified in women. A closer look at this APOE4 vulnerability in women revealed increased risk of conversion from normal to mild cognitive impairment (MCI) and from MCI to AD. Furthermore, female APOE4 carriers with MCI showed increased AD-associated biomarkers, such as cerebrospinal fluid tau levels and tau/Aβ ratios, compared with male carriers with MCI. However, some population-based studies have not observed female vulnerability to the APOE4-AD risk.

In this issue of JAMA Neurology, Neu et al probed the link between sex, APOE4, and AD risk with a high-powered, global meta-analysis that includes more than 57,000 patients aged 55 to 85 years from 27 independent research studies. In addition to power, their work adds the variable of time to our understanding of female vulnerability to APOE4. As expected, they confirmed that APOE4 carriers (ε3/ε4) showed increased risk for developing MCI, AD, and MCI conversion to AD, regardless of sex. Unexpectedly, they identified ages during which clinical, sex-based vulnerabilities emerge. Increased APOE4 risk in women compared with men was limited to ages 55 to 70 years for developing MCI and 65 to 75 years for developing AD.

In short, the Neu et al study appears to narrow the window through which we visualize increased AD susceptibility in women with APOE3/ε4. This finding raises the question: what is going on within and beyond this 10- to 15-year period? In a previous meta-analysis, AD risk among APOE4 carriers peaked and then eventually diminished at advanced ages, one reason that Neu et al may have observed a limited window of female vulnerability. Yet in the decades preceding this window, are deleterious APOE ε4 mechanisms preferentially operating in women? And within this window, does variable risk become more robustly detectable in a large, pooled cohort approach? Finally, what do these findings mean for women?

The Neu et al meta-analysis shows that female vulnerability to APOE4-associated AD risk is conserved across North America and Europe despite extensive variations inherent to populations separated by geographic distance and environmental conditions, factors that oftentimes obscure genetic associations. That is powerful and worth noting. However, an acknowledged limitation of the study is inclusion of primarily non-Hispanic white individuals. Furthermore, exclusion of studies with probable ascertainment bias, AD family history bias, and certain community populations may have constrained findings. Thus, it remains to be determined whether the conclusions, including a specific window of female vulnerability to APOE4, are generalizable to AD risk worldwide or across diverse heritage.

The emergence of clinical AD is a long pathophysiological process in the making. Thus, major influences on disease risk, such as APOE4, are operating for decades preceding clinical diagnosis. Importantly, the findings of Neu et al that women with APOE3/4 from age 65 to 75 years are at visible increased risk for developing AD means that the invisible effects of APOE4 are in action long before this age range. That is, the APOE ε4 protein probably dysregulates substrates of AD pathogenesis including neuronal and glial homeostasis, neural networks, mitochondrial function, and pathogenic proteins and their deleterious effects (Figure). This is important for women because APOE4 status may represent an opportu-
The emergence of clinical AD is a long, invisible pathophysiological process that becomes visible only after symptom onset. Thus, APOE ε4, one of the major influences on AD risk, is probably operating more in women compared with men for decades preceding clinical diagnosis, through mechanisms that are Aβ-dependent and Aβ-independent. This is important for women because APOE4 status may represent an opportunity for earlier, preventive intervention against development of AD.

Vulnerability for earlier, preventive intervention, particularly if we can advance mechanistic understanding to develop meaningful sex biology-based therapies.

Sex matters in brain health. Since 2011, endorsements or mandates by the National Institutes of Health, the Institute of Medicine, and other government agencies called for the incorporation of sex as a biologic variable to further investigate how it modifies brain health and disease. Once a sex difference in disease is reliably identified, such as the APOE4-AD risk in women as further validated by Neu et al., investigating its underpinnings is of major consequence to human health. Understanding what makes one sex more vulnerable (or more resilient) unravels exciting, new pathways we can target in novel treatments for 1 or both sexes. As we investigate sex biology in AD.

**REFERENCES**


