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Apolipoprotein E ϵ 4 and Risk Factors for Alzheimer Disease—Let's Talk About Sex

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The apolipoprotein E ϵ 4 (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?



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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, ϵ 2, ϵ 3, and ϵ 4, arise from a single locus on chromosome 19 and differ only in 2 discrete amino acid sequences (residues 112 and 158). Yet, this minute difference confers major consequences on molecular and physiological functions in the pathogenesis of AD.

Apolipoprotein E modifies A β -dependent and A β -independent mechanisms. The isoforms differentially regulate amyloid- β precursor protein transcription and A β production and secretion; APOE ϵ 4 exerts the most potent effect and APOE ϵ 2 the least.¹ This could explain, in part, why APOE ϵ 4 is deleterious. Similarly, the APOE isoforms differentially modify A β aggregation and clearance.² In addition to A β -dependent effects, strong evidence supports A β -independent roles for APOE ϵ 4 in the pathogenesis of AD including fragment toxicity, tau phosphorylation, synaptic vulnerability, and impairment of mitochondrial function.³

Are women more vulnerable to deleterious effects of APOE ϵ 4? In large-scale clinical^{4,5} and preclinical studies of risk, disease course and biomarkers,⁵ APOE4 carriers (ϵ 3/ ϵ 4) 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.⁵ Furthermore, female APOE4 carriers with MCI showed increased AD-associated biomarkers, such as cerebrospinal fluid tau levels and tau/A β ratios, compared with male carriers with MCI.⁵ However, some population-based studies have not observed female vulnerability to the APOE4-AD risk.

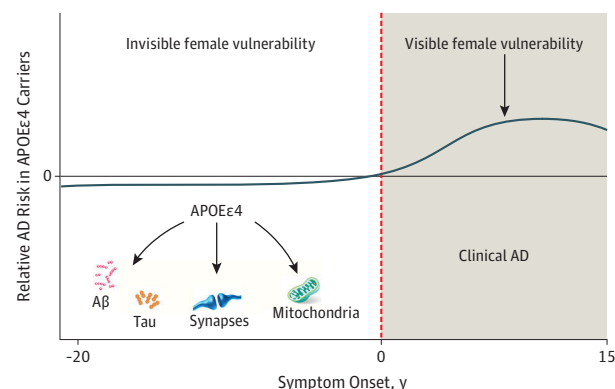
In this issue of *JAMA Neurology*, Neu et al⁶ probed the link between sex, APOE4, and AD risk with a high-powered, global meta-analysis that includes more than 57 000 patients aged 55 to 85 years from 27 independent research studies. In addition to power, their work adds the variable of time to our understanding of female vulnerability to APOE4. As expected, they confirmed that APOE4 carriers (ϵ 3/ ϵ 4) 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 study⁶ appears to narrow the window through which we visualize increased AD susceptibility for women with APOE3/E4. This finding raises the question: what is going on within and beyond this 10- to 15-year period? In a previous meta-analysis,⁴ AD risk among APOE4 carriers peaked and then eventually diminished at advanced ages, one reason that Neu et al⁶ may have observed a limited window of female vulnerability. Yet in the decades preceding this window, are deleterious APOE ϵ 4 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-analysis⁶ 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 al⁶ 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 ϵ 4 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-

Figure. Hypothetical Model of Apolipoprotein (APOE) ϵ 4-associated Vulnerability in Women and Increased Risk for Clinical Alzheimer Disease (AD)



The emergence of clinical AD is a long, invisible pathophysiological process that becomes visible only after symptom onset. Thus, APOE ϵ 4, 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 A β -dependent and A β -independent. This is important for women because APOE4 status may represent an opportunity for earlier, preventive intervention against development of AD.

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

Sex matters in brain health.^{7,8} 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.⁹ Once a sex difference in disease is reliably identified, such as the APOE4-AD risk in women as further validated by Neu et al,⁶ 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

granular detail, animal and cellular models are crucial and powerful tools to discover fundamental mechanisms. Practically, what does that look like in the research setting?

Marrying recent advances in APOE ϵ 4-mediated pathways^{1-3,10} to intelligent manipulations of sex biology^{7,11} creates an opportunity to dissect causes for and mechanisms of female vulnerability. For example, whether gonadal hormones or sex chromosomes mediate the APOE ϵ 4 sex difference or whether varying doses of X and Y chromosomes modify it can be directly tested with clever genetic manipulations. One such model enables generation of XX mice with ovaries or testes along with XY mice with ovaries or testes.¹¹ If XX mice were more vulnerable to the effects of APOE ϵ 4 (via knock-in) than XY mice, regardless of having ovaries or testes, then this would establish sex chromosomes as causal culprits. If so, modifying sex chromosome dosage could map APOE ϵ 4 vulnerability to the absence of Y or the presence of 2 X's. If, on the other hand, gonadal hormones governed the difference, further dissection of hormone type, receptors, and molecular pathways could reveal important signals in female vulnerability to APOE ϵ 4. These represent a few of many possibilities in investigating sex-based pathways of APOE ϵ 4, identifying key signals, and potentially targeting them for novel treatments. Thus, the study of sex differences can help us understand neurologic disease and develop therapies in a world where sex-based, personalized medicine is rapidly emerging.

The study by Neu et al⁶ importantly adds to our knowledge about APOE4 and AD risk in women. Their findings are timely, further validate female vulnerability in a large meta-analysis of defined populations, and inspire us to explain how 2 amino acid substitutions in APOE preferentially affect AD pathogenesis in women long before clinical manifestations. What if we could identify young women at high risk for AD decades before its onset, based on APOE4 status combined with other biomarkers, and offer a treatment derived from newfound, sex biology-based, APOE ϵ 4 pathways? And what if the treatment worked in men, too? This would represent monumental progress against AD, a major biomedical challenge with no truly effective medical therapies.

ARTICLE INFORMATION

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REFERENCES

- Huang YA, Zhou B, Wernig M, Südhof TC. ApoE2, ApoE3, and ApoE4 differentially stimulate APP transcription and A β secretion. *Cell*. 2017;168(3):427-441.e21.
- Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron*. 2009;63(3):287-303.
- Huang Y. Abeta-independent roles of apolipoprotein E4 in the pathogenesis of Alzheimer's disease. *Trends Mol Med*. 2010;16(6):287-294.
- Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA*. 1997;278(16):1349-1356.
- Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573.
- Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis [published online August 28, 2017]. *JAMA Neurol*. doi:10.1001/jamaneurol.2017.2188.
- Dubal DB, Broestl L, Worden K. Sex and gonadal hormones in mouse models of Alzheimer's disease: what is relevant to the human condition? *Biol Sex Differ*. 2012;3(1):24.
- Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimers Dement*. 2016;12(11):1186-1196.
- McCarthy MM, Arnold AP, Ball GF, Blaustein JD, De Vries GJ. Sex differences in the brain: the not so inconvenient truth. *J Neurosci*. 2012;32(7):2241-2247.
- Chung WS, Verghese PB, Chakraborty C, et al. Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. *Proc Natl Acad Sci U S A*. 2016;113(36):10186-10191.
- Mauvais-Jarvis F, Arnold AP, Reue K. A guide for the design of pre-clinical studies on sex differences in metabolism. *Cell Metab*. 2017;25(6):1216-1230.