Alzheimer's genetic risk tracked across sex, race

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A new study of genetic risks for cognitive impairment later in life uses data from 32,426 research participants aged 60 and older to elaborate risk across sex and across the intersection of sex and race. The study, the

largest of its kind to date, was reported July 17 in *JAMA Neurology*.

The risk variants at issue in the study occur in APOE, the gene that encodes the brain's principal cholesterol carrier, apolipoprotein E. In humans APOE comes in three variants. APOE3, the most common, is considered neutral with respect to Alzheimer's risk.

APOE4 is carried by half of people who develop Alzheimer's disease after age 65. It's known to increase risk more for women than for men, but apparently, it's been unclear whether this difference obtains across races. While common, APOE4 is considerably less common than APOE3.

APOE2, which is less common still, is considered to lower risk of cognitive impairment later in life, but apparently, it's been unclear whether APOE2 protection varies either with sex or with race.

"The prevalence of Alzheimer's disease differs by both sex and race. Learning more about how the cognitive effects of APOE, one of the most significant genetic risk factors for developing late-onset Alzheimer's disease, differ across sex and race can not only help inform research into the causes of cognitive decline in Alzheimer's disease, but also has incredibly important implications for personalized medicine," said the leader of the study, computational geneticist Logan Dumitrescu, Ph.D., MS, assistant professor of Neurology at Vanderbilt University Medical Center.

- The study finds that APOE4 has stronger negative effects on baseline memory and language capability in women than in men and establishes that this sex difference is similar for whites and Blacks.
- The study finds that risk reduction from APOE2 is similar for men and women overall, but when it comes to the intersection of

> sex and race, the researchers write that, for baseline executive function, "the APOE2 protective effect was female-specific among white individuals but male-specific among Black individuals."

"These are informative and somewhat surprising results," Dumitrescu said, "highlighting the fact that, while APOE2 and APOE4 have opposing effects on cognition and Alzheimer's disease risk, they are not simply two sides of the same coin, as they are differently modified by sex and race, which has implication for precision medicine, clinical trial inclusion, and underlying biological etiology."

Data for the study comes from four cognitive aging research cohorts, with 38% of participants found to carry at least one copy of APOE4 and 14% carrying at least one copy of APOE2. Cognitive performance was measured over time, and separate scores were highlighted for memory, executive function, and language capability.

More information: Skylar Walters et al, Associations of Sex, Race, and Apolipoprotein E Alleles With Multiple Domains of Cognition Among Older Adults, *JAMA Neurology* (2023). DOI: 10.1001/jamaneurol.2023.2169

Provided by Vanderbilt University

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