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Gene variant puts women at higher risk of Alzheimer's than it does men, study finds

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Carrying a copy of a gene variant called ApoE4 confers a substantially greater risk for Alzheimer's disease on women than it does on men, according to a new study by researchers at the Stanford University School of Medicine.

The scientists arrived at their findings by analyzing data on large numbers of older individuals who were tracked over time and noting whether they had progressed from good health to mild cognitive impairment—from which most move on to develop Alzheimer's disease within a few years—or to Alzheimer's disease itself.

The discovery holds implications for genetic counselors, clinicians and individual patients, as well as for clinical-trial designers. It could also help shed light on the underlying causes of Alzheimer's disease, a progressive neurological syndrome that robs its victims of their memory and ability to reason. Its incidence increases exponentially after age 65. An estimated one in every eight people past that age in the United States has Alzheimer's. Experts project that by mid-century, the number of Americans with Alzheimer's will more than double from the current estimate of 5-6 million.

According to the Alzheimer's Association, it is already the nation's most expensive disease, costing more than $200 million annually. (The epidemiology of mild cognitive impairment is fuzzier, but this gateway syndrome is clearly more widespread than Alzheimer's.)

The number of women with Alzheimer's far exceeds that of men with the condition. That's partly because women on average live longer than men. But greater longevity explains only part of women's increased susceptibility to Alzheimer's. "Even after correcting for age, women appear to be at greater risk," said Michael Greicius, MD, assistant professor of neurology and neurological sciences and medical director of the Stanford Center for Memory Disorders.

Greicius was the senior author of a study, to be published April 14 in the *Annals of Neurology*, in which he and his colleagues analyzed records on more than 8,000 people, most of them older than 60, who have been monitored over time at any one of about 30 Alzheimer's centers nationwide. Postdoctoral scholar Andre Altmann, PhD, was the lead author.

The records were stored in two large, publicly available repositories. In one, the researchers analyzed clinical assessments of 5,000 people whose test results were normal at the outset and 2,200 people who had initially showed signs of mild cognitive impairment. In both groups, being an ApoE4 carrier increased the likelihood of Alzheimer's disease, as expected. But a closer look revealed that among those who initially tested normal, this increased risk was only marginal for men, whereas women who carried the ApoE4 variant had close to twice the likelihood of progressing to mild cognitive impairment or Alzheimer's disease as those who didn't.

"Our study showed that, among healthy older controls, having one copy of the ApoE4 variant confers a substantial Alzheimer's disease risk in women, but not in men," Greicius said.

The second repository holds imaging data and measurements of several biochemical substances from spinal fluid that can serve as useful biomarkers of impending mild cognitive impairment and eventual

Alzheimer's disease. Analysis of 1,000 patients' records from this database not only confirmed ApoE4's differential effect on women versus men, but also yielded clues that may help investigators begin to explore, and perhaps someday explain, the molecular mechanisms linking ApoE4 to Alzheimer's disease, Greicius said.

The ApoE gene is a recipe for a protein important for shuttling fatty substances throughout the body. This is particularly important in the central nervous system, as brain function depends on rapid rearrangement of such fatty substances along and among nerve cell membranes. The ApoE gene comes in three varieties—ApoE2, ApoE3 and ApoE4—depending on inherited variations in the gene's sequence. As result, the protein that the gene specifies also comes in three versions, whose structures and fatty-substance-shuttling performance differ.

Most people carry two copies of the ApoE3 gene variant (one from each parent). But about one in five people carries at least one copy of ApoE4, and a small percentage have two ApoE4 copies. Numerous studies going back to the early 1990s have confirmed that ApoE4 is a key risk factor for Alzheimer's disease, with a single copy of ApoE4 increasing that risk twofold or fourfold. Carrying two copies confers 10 times the risk of Alzheimer's.

One of those many studies, published in 1997 in The *Journal of the American Medical Association*, suggested that female ApoE4 carriers are more at risk for Alzheimer's than male carriers are. But for various reasons, that study wasn't followed up, and both clinicians and scientists designing clinical trials tend to dismiss this distinction to this day, Greicius said. "I'd been practicing for five years before I ever heard of this paper, which had essentially been ignored for 10 years already," he said.

But on unearthing the 1997 paper, Greicius became curious. In 2012, an

imaging study by his group showed provocative differences in brain function in female versus male ApoE4 carriers even when they were still completely asymptomatic. "Brain connectivity in the ApoE4 men didn't differ much from normal. But connectivity in the ApoE4 women did," he said. "That convinced me that this is a real phenomenon."

The pooled data of numerous dedicated Alzheimer's centers continuously accumulates, yielding ever-larger population samples for enterprising researchers to mine. There lies the beauty of the large government- and industry-supported repositories to which Greicius and his team turned.

Drug developers designing clinical trials for Alzheimer's are already paying plenty of attention to whether or not their trial participants carry a copy of the ApoE4 variant, as previous trials have showed a differential effect on carriers versus noncarriers. Greicius said they would do well also to differentiate between a candidate drug's effect on male versus female ApoE4 carriers. Meanwhile, basic researchers can take a cue from his findings and ask themselves, "Why the difference?" The effort to answer that question may reveal an important molecular mechanism, or set of them, that explains the differential effect. "Now we can work toward understanding the cause of this sex difference, which may reveal new potential drug targets, "Altmann said.

Greicius, who in addition to his research spends about one-fifth of his time seeing patients, said that the differential male/female ApoE4 effect implies that clinicians need to take different approaches to patients with this gene variant, depending on their sex. "These days, a lot of people are getting genotyped either in the clinic or commercially. People come to me and say, 'I have an ApoE4 gene, what should I do?' If that person is a man, I would tell him that his risk is not increased much if at all. If it's a woman, my advice will be different."