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 billion annually. (The epidemiology of mild cognitive impairment is fuzzier, but this gateway syndrome is clearly more widespread than Alzheimer’s.)
Alzheimer’s risk higher for women

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, 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.

Protein recipe

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.

Continued on next page....
Gene variant cont’d

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.”

Wealth of data

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.”

For information about Stanford’s Department of Neurology and Neurological Sciences, which also supported this work, visit [http://neurology.stanford.edu](http://neurology.stanford.edu).
Other Stanford co-authors of the study were Lu Tian, ScD, associate professor of health research and policy, and Victor Henderson, MD, professor of health research and policy and of neurology and neurological sciences.

The study was funded by the National Institutes of Health (grant NS073498) and the JNA Foundation. Republished with permission from the Stanford School of Medicine’s Office of Communication & Public Affairs

---

**Brain Health Registry Launches at UCSF**

The Brain Health Registry -- led by top researchers at the University of California San Francisco -- is a groundbreaking, web-based project designed to speed up cures for Alzheimer’s, Parkinson’s and other brain disorders. It uses online questionnaires and online neuropsychological tests (similar to online brain games). The goal of the registry is to make clinical trials faster, better and less expensive. The project is scheduled for a public launch in the spring, but the researchers are inviting the public to be among the first to participate and provide feedback.

Why participate? The researchers offer the following reasons why everyone should register:

- **It’s easy.** It takes a few minutes to sign up and less than 3 hours per year. And it’s all done online, so registrants can do it from home -- or anywhere with Internet access.

- **The researchers say the registry offers an investigational breakthrough.** It is estimated that 85% of clinical trials have trouble recruiting enough participants. By creating a large online database of pre-qualified recruits, the Brain Health Registry can potentially cut the cost and time of conducting clinical trials. This is the first neuroscience project to leverage online possibilities in both this manner and scale.

- **It’s meaningful.** With every click of the mouse, you help researchers get closer to a treatment for Alzheimer’s and other brain diseases.

- **It’s safe.** Top scientists from some of the most respected institutions in medicine are leading the Brain Health Registry. They understand your need for privacy, and they will protect it at every step of the way. They are currently in their pre-launch phase. If you offer feedback -- and they hope you do -- they will read it, consider it carefully, and respond to you directly. You can help to improve their new website - they will be making many changes, based on your feedback, before their public launch.

For more information about the Brain Health Registry please visit [http://tinyurl.com/lvl8c8n](http://tinyurl.com/lvl8c8n)
Accountability Act Aims to Rectify NAPA Funding

The National Plan to Address Alzheimer’s Disease (NAPA) calls for a successful treatment for Alzheimer’s by 2025, but remarkably, does not provide funding to meet this goal. A bill introduced in Congress by Congressman Brett Guthrie (R-Kentucky) on April 1st, the Alzheimer’s Accountability Act of 2014, seeks to provide the much needed funding. First and foremost the Accountability Act would oblige the National Institutes of Health to submit an annual budget to Congress specifying the dollar amount required to meet each milestone of the national plan. The proposed act does not appropriate any money.

“The Accountability Act tries to make the national plan more amenable to step-by-step accomplishment by Congress. It’s a move in the right direction,” said Ron Petersen, who chairs the Advisory Council appointed by the National Alzheimer’s Project Act (NAPA).

The new act is intended to prod Congress, according to fellow council member George Vradenburg of the advocacy group USAgainstAlzheimer’s.

The Advisory Council’s recently released 2014 recommendations estimated at $2 billion annually in order to meet the goals of the National Plan. Alzheimer’s disease currently receives around half a billion dollars in total funding, about a tenth of the money allocated to cancer, according to NIH statistics. Congress allocated an additional $50 million in Alzheimer’s research funding in 2012, $45 million in 2013, and $80 million in 2014, but many involved in Alzheimer’s research see this as a drop in the bucket. At present the president’s proposed 2015 budget does not offer any new funding for Alzheimer’s according to Petersen.

The council’s 2014 guidance also advises a few notable changes to the National Plan such as reforming clinical trials to speed up drug testing, studying ways to improve the early diagnosis of AD, and adding research milestones for other forms of dementia, such as frontotemporal, Lewy body, and vascular dementia. The council also proposed that the U.S. help create a Global Alzheimer’s Action Plan, in keeping with goals expressed at the G8 Dementia Summit in London in December 2013.

-ADIN
Do Earliest Cognitive Deficits in Alzheimer’s Appear in the Entorhinal Cortex?

Reprinted with permission from AlzForum

11 Apr 2014

With the increasing focus on preclinical disease, scientists want to know what goes wrong first in AD brains, and where. In the April 9 Journal of Neuroscience, researchers led by Willem Huijbers and Reisa Sperling at Brigham and Women’s Hospital, Boston, report that amyloid deposits in the neocortex correlate with a failure to dial down the activity of the entorhinal cortex during memory tasks. These changes occur before any overt memory problems or hippocampal deficits, and are distinct from age-related decline, the authors found. The findings point toward the entorhinal cortex as a potential target for prevention studies, Huijbers suggested.

“This is a very nice paper that ties Aβ in the neocortex with dysfunction in the medial temporal lobe. In the past, it has been difficult to connect these two stories,” said William Jagust at the University of California, Berkeley. He was not involved in the work. The medial temporal lobe, which includes the entorhinal cortex, controls memory formation and contains mostly tau pathology early in AD.

Previous studies by Sperling’s group and others have shown that amyloid accumulates first in the default mode network (DMN), a set of connected regions largely in the neocortex that are active when the brain is at rest (see Feb 2009 news story). As this network becomes clogged with amyloid, its activity wanes (see Mar 2004 news story). Less is known, however, about how early amyloid deposits affect the functions of the hippocampus and entorhinal cortex. In some studies, these medial temporal lobe regions synchronize their activity with the DMN, suggesting a close connection.

Huijbers and colleagues wanted to investigate the relationship between neocortical amyloid and memory. Since memory also fades in normal aging, the authors first compared brain activity during a memory task in young and old volunteers. They recruited 48 participants around 75 years old, as well as 21 who were about 25, from the Harvard Aging Brain Study. The volunteers, all cognitively normal, first tried to memorize 150 face-name pairs with random first names. Then they were shown those pairings along with 150 new face-name pairs while their brains were scanned using functional MRI. Participants had to indicate whether they had seen each pair before. This paradigm allowed the researchers to see how brain activity changed when the volunteers recognized or failed to recognize a familiar pair, as well as when they memorized or failed to memorize a new pair. Brain activity was judged by changes in brain blood flow (blood-oxygen-level dependent, or BOLD, signal).

During both memorization and recognition tasks, participants activated several brain regions that included the hippocampus, while simultaneously quieting the DMN and entorhinal cortex. Older adults were less able to turn on the hippocampus and to squelch EC activity than were young adults, the researchers found (see image below). This difference in brain activity correlated with poorer performance on the task. The older participants recognized 57 percent of the known face-name pairs, significantly worse than the 63 percent that young volunteers got right. 

Cont’d on next page...
The pattern of regional brain activation (yellow) and deactivation (blue) during a memory task becomes less precise with age. [Courtesy and with permission of Huijbers et al., The Journal of Neuroscience, 2014.]

How does the presence of amyloid change the picture? To determine this, the authors divided the older cohort into people with or without Aβ accumulation in their neocortex as seen by PIB-PET imaging. Those with amyloid scored just as well as those without on the memory task, but fMRI revealed differences in brain activity. While hippocampal activation was similar in both groups, those with amyloid had significantly more trouble turning off the EC during the memory task. This problem was worst when memorizing new face-name pairs, but also occurred when recognizing known pairs, and remained even after correcting for the effects of age, gender, brain atrophy, and ApoE genotype. The results suggest that Alzheimer’s strikes first in the EC, before it affects hippocampal function. This agrees with other studies (see Dec 2013 news story).

“It’s been difficult to show behavioral effects in healthy people who have amyloid,” noted Denise Park at the University of Texas, Dallas. “This paper used a very clever design to separate the effects of healthy aging from amyloid pathology. It’s a good model for how we can use fMRI to understand what neural circuits are affected earlier and later by amyloid.”

What factors might link amyloid in the neocortex to functional deficits in the entorhinal cortex? One possibility is that neurofibrillary tangles account for the EC’s sluggish response. The EC develops tau tangles during normal aging. This pathology accelerates in AD and likely precedes neocortical amyloid deposits (see Nelson et al., 2012). Thus, people with amyloid in the DMN should also have substantial tangles in EC. Huijbers plans to follow the participants for five more years using both amyloid and tau imaging to try to disentangle the effects of these two pathologies.
Alternatively, sputtering connections in the DMN may isolate the EC and weaken its ability to switch off in response to activity elsewhere. Huijbers and colleagues found that EC activity synchronized closely with DMN activity during the face-name task, while the hippocampus did not. Moreover, the EC meshed less well with the DMN in people with brain amyloid than in those without, although the trend did not reach statistical significance. The data hint that an overall loss of brain connectivity might underlie the earliest cognitive deficits in people on the path to AD. This fits with other data showing that people with Alzheimer’s experience a general breakdown of brain networks and lose the ability to switch smoothly between them.

The findings may focus more attention on EC connectivity, said Howard Aizenstein at the University of Pittsburgh. “The dissociation between the entorhinal cortex and hippocampus proper is interesting, and this paper is the first to show that functionally,” he told Alzforum. Aizenstein wondered if EC dysfunction might eventually serve as a biomarker for clinical research, identifying those people with amyloid who will progress most quickly. Researchers agreed, however, that complex fMRI measures like this are unlikely to make good biomarkers for clinical practice.

—Madolyn Bowman Rogers, AlzForum
A Possible New Blood Test for AD?

By Michael Rafii, MD, PhD
UC San Diego

According to a study recently published in the journal, Nature Medicine, a team of researchers has identified 10 lipids in the blood that may be able to detect the early signs of Alzheimer's disease (AD).

The study included 525 healthy participants aged 70 and older who gave blood samples upon enrolling at various points in the study. Over the course of the five-year study, 74 participants met the criteria for either mild AD or mild cognitive impairment (MCI). Of these, 46 were diagnosed upon enrollment and 28 developed MCI or mild AD during the study (the latter group called converters).

In the study's third year, the researchers selected 53 participants who developed aMCI/AD (including 18 converters) and 53 cognitively-normal matched controls for the lipid biomarker discovery phase of the study. The lipids were not targeted before the start of the study, but rather, were an outcome of the study.

They discovered a panel of 10 lipids, which researchers say appears to reveal the breakdown of neural cell membranes in participants who developed symptoms of cognitive impairment or AD. The panel was subsequently validated using the remaining 21 MCI/AD participants (including 10 converters), and 20 controls. The lipid panel was able to distinguish with 90 per cent accuracy these two distinct groups – cognitively normal participants who would progress to mild cognitive impairment or Alzheimer’s disease within two to three years, and those who would remain normal over the same time interval.

The study has garnered a significant amount of attention, as the need for an easy, inexpensive, and accurate test for AD cannot be found soon enough. However, it should be kept in mind that the findings of the paper are part of a long standing effort by researchers who have been working for at least a decade on a blood test for AD. For this finding to be truly stand apart from the rest, the lipid panel's predictive power will need to be confirmed in a larger sample of participants.

Continued on next page...
The accumulation of beta-amyloid seems to be the driving force behind brain cell injury in AD, leading to a cascade of events that further damage brain cells and compromise cognitive function. As the disease worsens and more neurons die off, atrophy or shrinkage of brain tissue occurs. Some of the most reliable tests in the field include measurements of brain atrophy with volumetric MRI, measures of beta-amyloid in the spinal fluid and detection of amyloid with amyloid PET scans. The premise behind a blood test would be to find a surrogate in the blood for these brain changes. Many have looked at beta-amyloid itself, as well as markers of inflammation. This most recent paper raises the possibility that we may be closer to finally having a blood-based test for AD.
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/clinalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

Enrolling soon:

NOBLE
A New Study for People with Mild to Moderate Alzheimer’s Disease
The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.