by Megan Brooks

January 12, 2012 - Maintaining a physically activee lifestyle may be particularly beneficial in reducing the risk for Alzheimer's disease (AD) in the individuals most at risk: those with the ε4 allele of the apolipoprotein E (*APOE*) gene.

In a study of cognitively normal adults, exercising at levels recommended by the American Heart Association (AHA) was associated with less brain amyloid deposition, with stronger associations seen in *APOE* ε4 carriers than in noncarriers.

The findings in this study are "somewhat suggestive that exercise engagement may be potentially preventive," Denise Head, PhD, from the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis, Missouri, who worked on the study, told *Medscape Medical News*
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Their report was published online January 9 in the *Archives of Neurology*.

Novel Interactions

The presence of an *APOE* ε4 allele is a well-established genetic risk factor for AD, with a higher percentage of individuals with AD having an ε4 allele in comparison with the general population, the study team notes in their article. It has been suggested that
APOE
status may modify associations between lifestyle factors such as physical activity and risk for cognitive decline and dementia.

To investigate further, Dr. Head and colleagues examined the association between exercise and cerebral brain amyloid deposition in 201 men and women, both with and without the *APOE* ε4
allele, from the ADRC. The study participants were between 45 and 88 years old and had normal cognitive function.

Cerebrospinal fluid (CSF) was collected and analyzed from 165 participants, and positron emission tomography (PET), using the amyloid-binding agent Pittsburgh compound B, was performed in 163 participants.

All patients provided information on their exercise habits over the course of the last 10 years and were categorized into low- and high-exercise groups based on whether their reported exercise levels were at or above the 7.5 metabolic equivalent hours per week (30 minutes of moderate exercise 5 days/week) recommended by the AHA.

The researchers found significant differences in amyloid deposition (mean cortical binding potential [MCBP]) by exercise group ($P < .001$) and *APOE* status ($P < .001$).

Individuals in the high-exercise group (those who met AHA recommendations) had lower MCBP compared with those in the low-exercise group, and *APOE* ε4 carriers had higher MCBP compared with noncarriers.

"Most importantly," say the researchers, there was a "novel interaction" between *APOE* status and exercise group for MCBP ($P = .008$) - one reflecting a ggreater effect of exercise on MCBP in *APOE* ε4 carriers than noncarriers.

A more sedentary lifestyle was significantly associated with higher MCBP for *APOE* ε4 carriers ($P = .013$), but not for noncarriers ($P = .20$), the researchers say.

"In fact, post hoc analyses indicate that the magnitude of MCBP was equivalent between active ε4-positive individuals and all ε4-negative individuals ($t = 0.07$; $P = .41$), and between active ε4-positive individuals and active ε4-negative individuals (

t
= –0.722;
P
= .24)," they report.

"The MCBP findings support the idea that a physically active lifestyle may allow ε4 carriers to experience brain amyloid levels equivalent to ε4-negative individuals," the investigators add.

"Notably," the results "remained robust" after controlling for age, sex, education level, body mass index, and the presence or history of hypertension, diabetes, cardiac problems, and depression, the researchers say.

Collectively, Dr. Head told *Medscape Medical News*, "the combination of a sedentary lifestyle and the established genetic risk factor (ie,
APOE
ε4-positive status) may be associated with augmented risk for some types of AD-related pathology."

Unexpected Observation

Overall, the results were "largely consistent with our expectations," Dr. Head said, with 1 caveat: There was no interaction between *APOE* status and exercise for CSF β-amyloid 42 level.

"A stronger association between exercise engagement in *APOE* ε4-positive individuals compared to *APOE*
ε4-negative individuals was only present for the 1 PET-based measure of amyloid deposition, but not for the other CSF-based measure," Dr. Head said.

"This was unexpected," she noted, given that the 2 markers largely reflect complimentary estimates of the same process of amyloid plaque development in the brain, and are strongly associated.

The mechanisms through which exercise may influence amyloid deposition remain unclear, but may include direct effects on amyloid precursor protein metabolism and indirect effects through influences on neurotrophic factors, neuroinflammation, cerebrovascular functioning, and glucose metabolism, the researchers note in their article.

"There are all kinds of theoretical links here," Creighton H. Phelps, PhD, director of the Alzheimer's Disease Centers Program in the Division of Neuroscience at the National Institute on Aging, who was not involved in the study, noted in an interview with *Medscape Medical News* .

"For example, we know that *APOE* ε4 status affects the plasticity or healing properties of the synaptic areas of the brain - they don't seem to remodel as quickly - and we know that exercise in general does inccrease growth factors, and growth factors stimulate plasticity and remodeling," he said.

Overall, Dr. Phelps said the findings reinforce that "exercise can reduce the amount the amyloid in the brain, and that *APOE* ε4-positive status can increase the amount of amyloid in the brain. The biggest finding in the study is that exercise can diminish the amount of amyloid in *APOE* ε4-positive people."

Dr. Phelps noted that the study was cross-sectional, with self-reporting of exercise, and that "a larger, longitudinal study is needed," with monitoring of participants activity levels.

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