Too Young to Worry?

EARLY PREDICTION OF ALZHEIMER'S DISEASE RISK

Alzheimer's disease (AD) risk increases with age, and symptoms typically appear in individuals who are 60 years of age and older. As a result, many of us do not tend to give much thought to AD or protective lifestyle measures in early adulthood.

However, certain cardiovascular markers associated with AD risk may be predictive as early as in our mid-30s, according to a recent study conducted by researchers from the Boston University School of Medicine.

> THE STUDY FOUND THAT LOWER HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL AND ELEVATED GLUCOSE LEVELS AS EARLY AS AGE 35 WERE ASSOCIATED WITH A HIGHER RISK OF DEVELOPING AD IN LATER LIFE.

The findings, published in March 2022 in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, suggest that it is essential to be aware of these health markers starting in early adulthood and that careful management to address these issues may potentially lower the risk of developing AD in later years.

"It's well understood that certain cardiovascular and metabolic health conditions, including high cholesterol, diabetes, obesity, high blood pressure, and metabolic syndrome, are predictive risk factors for AD. However, most of that knowledge came from studies of individuals who were 55 to 60 years old at baseline," said senior study author Dr. Lindsay Farrer, Chief of Biomedical Genetics and Distinguished Professor of Genetics at the Boston University School of Medicine.

"To our knowledge, our study is the first to report associations between AD and HDL cholesterol and glucose levels in earlier adulthood."

STUDY CONTEXT

For their study, Dr. Farrer and colleagues used data from the Framingham Heart Study (FHS), a multigenerational, long-term study that has been collecting blood samples, physical examination data, and diagnostic information from residents of Framingham, Massachusetts since 1948.

The initial goal of the FHS was to identify common factors contributing to heart disease, but the study has enabled a treasure trove of insights for other health conditions over time.

Nearly 5,000 study participants, aged 20 to 49 at intake, were examined every four years from 1971 through 2016. The participants were evaluated for cognitive decline and dementia, commencing in 1979, including with the Mini-Mental State Examination (MMSE) starting in 1991 and in-depth cognitive examinations beginning in 1999.

The investigators defined the age of AD onset as the earliest recorded date of cognitive impairment. They calculated whether lipid fractions, glucose, blood pressure, body mass index (BMI), and smoking were associated with AD risk for three groups of study participants: early (ages 35 to 50), middle (ages 51 to 60), and late (ages 61 to 70) adulthood.

KEY FINDINGS

- Higher HDL cholesterol was associated with lower AD risk in early and middle adulthood. A 15 mg/dL increase in HDL cholesterol was associated with an approximately 15% lower risk of developing AD for adults ages 35 to 50 and an approximately 18% lower risk for adults ages 51 to 60.
- Elevated blood glucose was associated with higher AD risk in middle adulthood. A 15 mg/dL increase in glucose measured between the ages of 51 to 60 was associated with a nearly 15% increased risk of developing AD.
- BMI, low-density lipoprotein (LDL) cholesterol, systolic blood pressure, and smoking were not related to AD risk in any age group.

THE RESEARCHERS LOOKED FOR DIFFERENCES IN RESULTS BETWEEN WOMEN AND MEN AND OBSERVED SIMILAR PATTERNS OF ASSOCIATION.

However, there were only 247 cases of AD – an insufficient number for demonstrating a statistically meaningful difference between women and men, Dr. Farrer explained.

EXPERTS WEIGH IN

"The information for our study was collected prospectively over decades, a key strength of the FHS," said Dr. Farrer. "However, the findings don't prove cause and effect. They point to associations from which we can make inferences and generate hypotheses to test experimentally."

Dr. Allison Reiss, Associate Professor of Medicine at the NYU Long Island School of Medicine and a member of the Alzheimer's Foundation of America's Medical, Scientific, and Memory Screening Advisory Board (who was not involved in the study) agreed: "The main findings and implications of the study are good messages, but the findings are associations, not causal relationships. Much work needs to take place to understand these relationships better."

Evidence from other studies may shed light on some of the hypotheses that may explain the findings. For example, other →

LEARN MORE ABOUT ALZHEIMER'S DISEASE & WOMEN

The Alzheimer's Foundation of America (AFA) recently produced "AFA Fireside Chats," an eight-part educational web series to raise Alzheimer's disease (AD) awareness. Each episode features a discussion with an expert from AFA's Medical, Scientific, and Memory Screening Advisory Board.

Episodes are available for free online at alzfdn.org/firesidechat/.

Watch Episode 7 (entitled "Healthcare Disparities for Women") to see Dr. Allison Reiss discuss the disproportionate impact of AD on women and the steps that women can take to reduce their risk and overcome obstacles to care.

scientists have demonstrated in laboratory studies that HDL plays a role in reducing the accumulation and inflammation caused by amyloid-beta, one of the abnormal hallmark proteins thought to be involved in AD.

They have also found that HDL may help reduce amyloid-beta accumulation by transporting it through blood vessels. Finally, an inherited genetic variation, the APOE e4 allele, reduces HDL cholesterol and is known to be associated with a higher risk of AD in adults over the age of 65.

"I suspect the association between a higher HDL and lower AD risk indicates an underlying problem further upstream," said Dr. Reiss. "Emerging evidence shows that the quality of HDL, which was not investigated in the present study, is also important. Medications can boost production of HDL, but if that HDL is of poor quality, it's not helpful."

Scientists have already identified a link between higher glucose levels and elevated AD risk in studies of older adults.

For example, a study published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in March 2018 found that increases in fasting blood glucose were associated with a higher accumulation of amyloid-beta plaques and tau tangles and impaired glucose metabolism in the brain in an autopsy cohort of the Baltimore Longitudinal Study of Aging.

HIGH BLOOD GLUCOSE MAY CONTRIBUTE TO AN ELEVATED RISK OF AD IN DIFFERENT WAYS.

For example, Dr. Farrer and his research team noted evidence from other studies that showed excess glucose could exacerbate neuroinflammation caused by amyloid-beta, alter immune responses in the brain through a process called glycation (in which sugar molecules attach to proteins and cause them to behave abnormally), and make neurons insulin resistant.

"Excess glucose is toxic to neurons, with inflammation playing a big role in causing damage," said Dr. Reiss. "Glycation ruins proteins and also hurts blood vessels in the body, linking back to vascular health issues associated with AD risk."

The researchers also adjusted their results for diabetes, hypertension, and dyslipidemia treatments. "Our findings were somewhat attenuated, but the associations we identified didn't disappear, suggesting that an earlier foundation of risk factors plays a role in the longer-term development of AD," explained Dr. Farrer.

Finally, Dr. Farrer noted that lifestyle factors alone are not solely to blame for the AD risk factors they identified. "Genetic differences can also affect cholesterol levels, glucose levels, blood pressure, and other cardiovascular factors associated with a higher risk of AD and other cognitive health issues."

THE BOTTOM LINE

"Older adults are well aware of the need for annual health checkups, but millennials, for example, tend to assume they are healthy and skip them," said Dr. Farrer. "We hope our findings will encourage more people in their 30s and older to have annual checkups and get screened for blood glucose and lipid levels."

> *Earlier awareness of risk factors may allow them to take steps to prevent AD and other conditions as they age.*

"Once an individual has symptoms of cognitive decline resulting from neurons that have died, those neurons cannot be brought back to life," said Dr. Reiss. "A far better strategy is to keep them from dying in the first place by taking good care of yourself in younger years and reap the dividends later. Don't wait yourself out."

FUTURE DIRECTIONS

Dr. Farrer and Dr. Reiss both agreed that more research is necessary to understand upstream mechanisms that may explain exactly how lower HDL cholesterol and higher glucose raise AD risk. In their respective laboratories, they are actively seeking underlying molecular mechanisms that cause neuronal loss in AD, hoping to identify effective treatment strategies.

"Once amyloid-beta and tau accumulate, it's like a crumbling building. Medications may sweep out the debris, but the building is still falling apart," said Dr. Reiss. "These hallmark proteins are a sign of a degradation process in AD, not the cause, which may be why so many treatments targeting them have failed to produce compelling results in clinical trials."

Dr. Farrer also continues to search for genetic factors that raise AD risk, including those that may be sex specific. Together with colleagues at the Boston University School of Medicine and the University of Chicago, he recently discovered that a new gene called "MGMT," which plays a role in repairing DNA damage, was significantly associated with the development of amyloid-beta and tau proteins in women more so than in men.

In their paper, published in June 2022 in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, the researchers noted that further studies are needed to better understand how and why MGMT is associated with higher AD risk in women.