Multiple dementia risk factors lead to greater chance of cognitive decline, study finds

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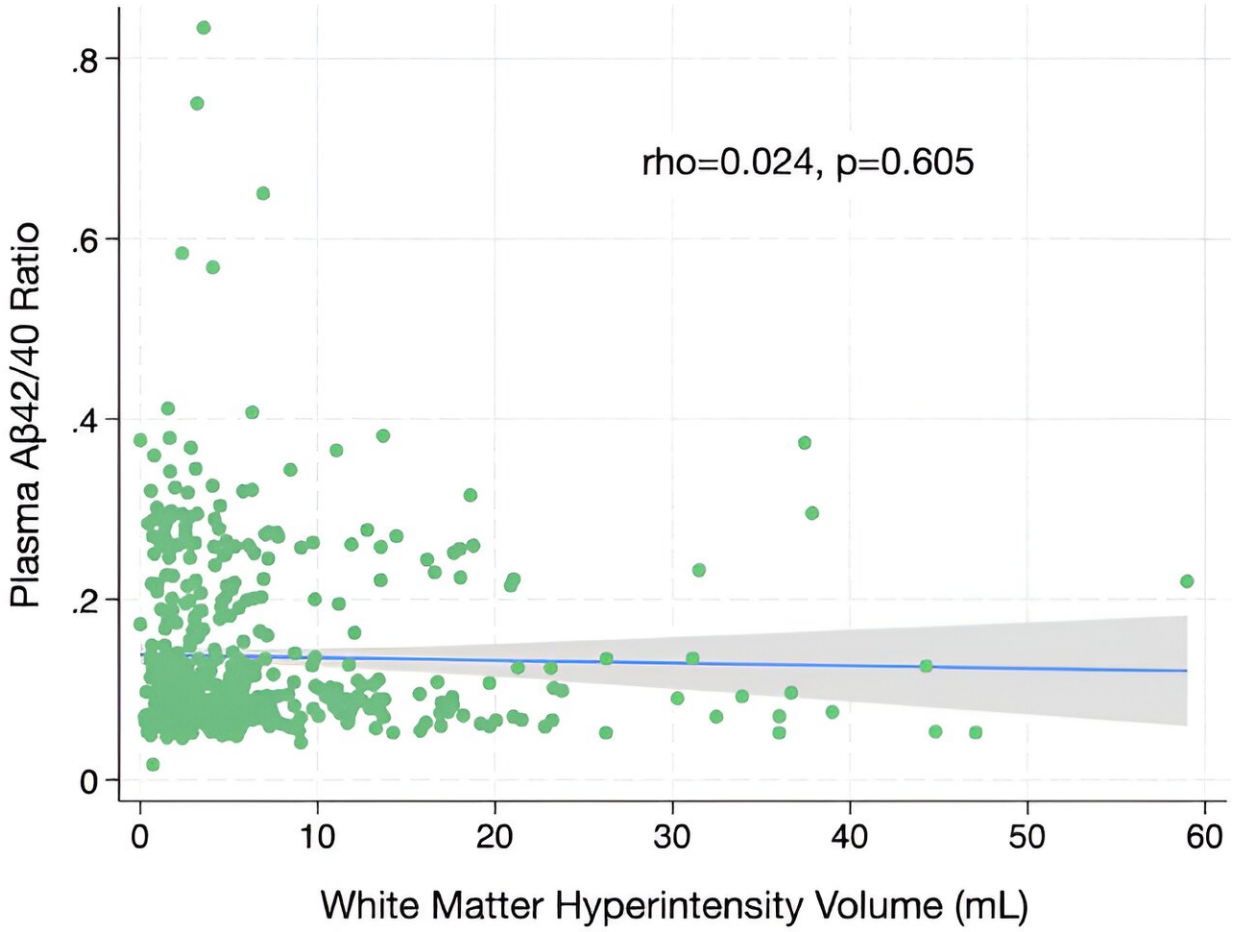

Scatter plot and linear fit with 95% confidence interval between white matter hyperintensity in mL and plasma amyloid beta (Aβ)42/40 ratio. Credit: *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.14126

Cognitive decline and dementia can stem from illnesses like Alzheimer's disease and conditions like hypertension that damage blood vessels in the brain. People with both may have an even greater risk of developing cognitive impairment, a new Yale study finds.

This additive effect, say researchers, will likely have an outsized impact on medically underserved populations, which makes it imperative that racially diverse trials be conducted to evaluate how to treat both contributions to dementia effectively.

For the study—published Sept. 4 in *Alzheimer's & Dementia*—the researchers used data from the Systolic Blood Pressure Intervention Trial, which took place between 2010 and 2015 and included adults aged 50 or older with hypertension. All told, the new study included data from 467 racially diverse trial participants aged 60 or older.

Two biomarkers served as proxies for the vascular- and Alzheimer's-related contributions to cognitive impairment. The first—white matter hyperintensity—which is a biomarker for brain scarring caused by damage to small blood vessels in the brain often due to high blood pressure, was measured via MRI when participants joined the trial.

"White matter hyperintensity means that when we look at the brain via MRI, the white matter, or the nerve connections between different regions of the brain, shows up as extra white," said Dr. Adam de Havenon, an associate professor of neurology at Yale School of Medicine and lead author of the study. "We see it as scarring of the neurons when we look at the brain during autopsies of individuals who had vascular dementia."

Alzheimer's disease is marked by the formation of amyloid plaques, aggregates of a protein called amyloid-beta that collect in the brain. The plaques can be seen during post-mortem analyses but can't be directly

measured non-invasively. An alternative is to measure the ratio of two peptides—Abeta42 and Abeta40—that circulate in the blood and correlate with amyloid-beta levels in the brain.

The researchers evaluated which participants had scores representing the highest and lowest risks of brain scarring and amyloid plaque buildup during the first evaluation as well as who developed cognitive impairment over the following four years.

"We found that the risk of developing cognitive impairment was considerably higher for the participants who had more white matter hyperintensity and more amyloid-beta than for those who just had one or the other," said de Havenon.

Specifically, the researchers found that those with the lowest risk scores for white matter hyperintensity and amyloid-beta also had the lowest rates of cognitive impairment (5.3%). Those with high scores for one risk factor but low scores for the other had higher rates of cognitive impairment (7.8% for white matter hyperintensity and 11.8% for amyloid-beta). And participants with high scores for both risk factors had the highest rates of cognitive impairment at 22.6%.

"That tells us that both are risk factors independently and together lead to even greater risk," said de Havenon.

One reason researchers are only beginning to understand the relationship between these two risk factors is because studies tend to focus on one or the other, de Havenon added.

"In general, causes of dementia are siloed in research," he said. "But for most patients, cognitive impairment and dementia aren't just caused solely by Alzheimer's disease or solely by vascular issues. For most it's a mix of both and other things like lived environment, education, and how

many contact sports they played."

To really understand how these two risk factors together contribute to cognitive impairment, says de Havenon, there need to be clinical trials that aim to treat both. And those trials should be racially and socioeconomically diverse so that the findings are generalizable to the wider population and include groups more likely to be affected by dementia risk factors.

As de Havenon explains, more advantaged populations are likely to have the resources to treat health issues like hypertension that can lead to vascular dementia. Underserved populations that lack those resources, therefore, carry a greater burden of vascular contributions to cognitive impairment.

Now that treatments are becoming available to reduce amyloid-beta progression, researchers expect Alzheimer's disease burden will also shift toward underserved populations.

"This is a health equity issue," said de Havenon. "We have to conduct trials that look at treating both amyloid and hypertension. It's the only way we can avert the growing health disparities in dementia."

More information: Adam de Havenon et al, White matter hyperintensity on MRI and plasma Aβ42/40 ratio additively increase the risk of cognitive impairment in hypertensive adults, *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.14126

Provided by Yale University