Study links lack of diversity in Alzheimer's disease clinical trials to differences in amyloid levels

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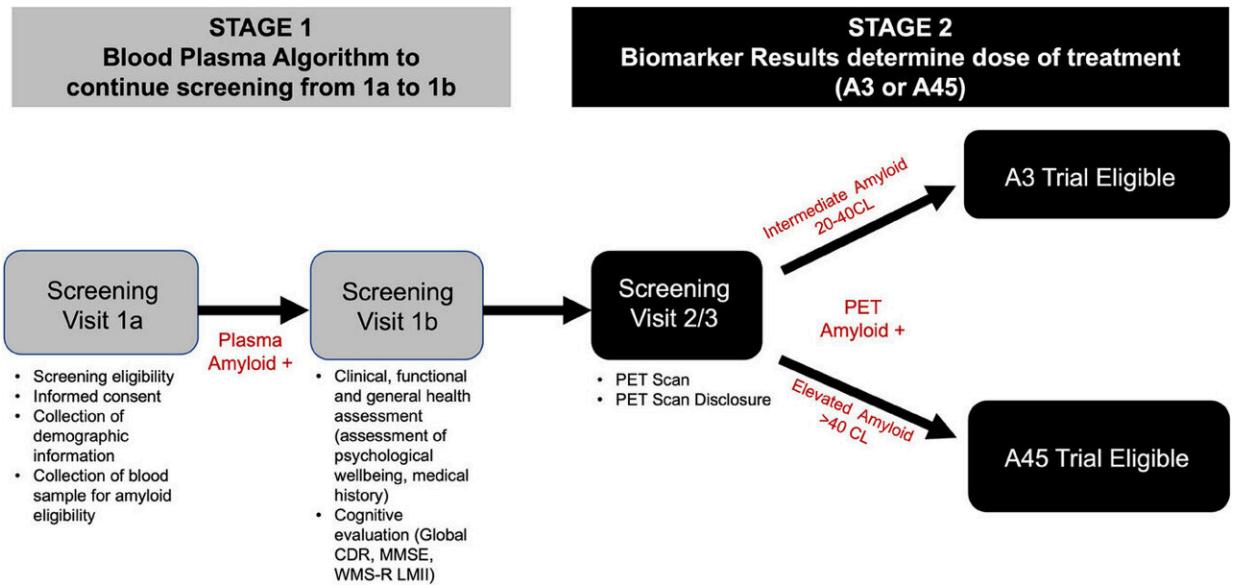

AHEAD A3-45 Study sister trials with a common screening process. Randomization to A3-A45 after Stage 2 is dependent on levels of PET amyloid. CDR, Clinical Dementia Rating; CL, Centiloids; MMSE, Mini-Mental State Examination; PET, positron emission tomography; WMSR-LMS II, Wechsler Memory Scale-Revised Logical Memory Subscale II. Credit: *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.13803

It's long been recognized that some of the groups most likely to get dementia, including African Americans and Hispanics, are greatly

underrepresented in clinical trials. Now a new USC study shows that people from certain racial and ethnic groups may be ineligible for Alzheimer's disease clinical trials because they have lower levels of amyloid protein at early stages of the disease. The study also suggests that Alzheimer's may progress differently in different populations.

The work is published in the journal *Alzheimer's & Dementia*.

Researchers from the Keck School of Medicine of USC collected blood tests and brain scans from 4,905 participants, ages 55 to 80. Based on blood tests designed to detect levels of amyloid, the protein known to disrupt brain activity in Alzheimer's disease, people who identified as non-Hispanic whites were most likely to meet eligibility cutoffs for clinical trials.

People who identified as Hispanic Black, Hispanic white, non-Hispanic Asian and non-Hispanic Black were significantly less likely to be eligible for studies based on amyloid levels in the blood when compared to non-Hispanic white counterparts.

Participants who were eligible based on blood tests also underwent positron emission tomography (PET) scans, brain scans that are used to directly measure amyloid buildup in the brain. Among "plasma-eligible" participants (those who met the blood test cutoff), individuals from all racial and ethnic groups were equally likely to be eligible to participate based on PET scan data.

"In these early stages, we see that the amyloid levels are different across racial and ethnic groups. That may be an important contributor to the underrepresentation of some groups in amyloid-lowering trials," said Doris P. Molina-Henry, Ph.D., an assistant professor of research neurology at the Alzheimer's Therapeutic Research Institute (ATRI) at the Keck School of Medicine and lead author of the study.

Participants in the study were considered preclinical, meaning they did not have cognitive impairment characteristic of Alzheimer's disease or another form of dementia, but did have some biological changes related to the condition (in this case, amyloid proteins in the blood). A growing number of clinical trials seek to intervene during this stage, either by removing amyloid protein from the brain or preventing it from building up.

The findings add to existing research suggesting that in different populations, different factors may contribute to cognitive decline. Unknown factors may make some individuals more vulnerable to symptoms of dementia, even if their amyloid levels remain low, and future research should aim to understand why, said Molina-Henry.

"This opens up further questions: If it's not amyloid that's driving Alzheimer's disease, what is it? Or if amyloid is driving this, what is making the brain of someone from a group at higher risk for dementia much more susceptible?" she said.

Clinical trial eligibility

As part of the AHEAD 3-45 study, a clinical trial designed to test the safety and efficacy of the medication lecanemab, researchers had access to preclinical Alzheimer's disease participants at 75 sites across the country. The research team placed a special emphasis on recruiting and enrolling individuals from racial and ethnic groups that are traditionally underrepresented in Alzheimer's research.

The study included 4,905 adults, ages 55 to 80, without cognitive impairment or dementia: 60 Hispanic Blacks, 671 Hispanic whites, 101 non-Hispanic Asians, 381 non-Hispanic Blacks and 3,692 non-Hispanic whites.

The researchers collected blood from each participant and calculated amyloid levels, using a liberal threshold to determine who was considered eligible for inclusion in the clinical trial. The trial requires a participant to have 20 centiloids or more of amyloid, but researchers lowered the cutoff to 11 centiloids to avoid excluding participants who might be just below the typical threshold. Centiloids are units in a standardized method of measuring amyloid plaque in the brain based on PET imaging.

Of the 4,905 adults tested, 1,724 (35.1%) were "plasma-eligible" to participate in a clinical trial, meaning they met the 11-centiloids blood test cutoff. Broken down by racial and ethnic group, non-Hispanic whites had the highest rate of eligibility at 38.9%. All other groups were significantly less likely to meet eligibility criteria: just 13.3% of Hispanic Blacks, 24.7% of Hispanic whites, 20.8% of non-Hispanic Asians and 24.7% of non-Hispanic Blacks surpassed the 11-centiloids threshold.

Then, the researchers collected and analyzed PET scans from the 1,724 participants who were deemed plasma-eligible for the clinical trial. All racial and ethnic groups in the study were equally likely to meet inclusion criteria based on PET scans.

"This suggests that the cutoffs for eligibility are adequate, but also point to a paradox where some groups may have a higher risk of dementia but lower levels of amyloid, and treating those groups may require a different approach," Molina-Henry said.

Improving access

The study raises several questions about what factors may impact Alzheimer's disease progression in various racial and ethnic groups. For example, are some groups more vulnerable to dementia, even with lower

levels of amyloid? Do comorbid conditions, such as cardiovascular disease, play a key role in Alzheimer's disease progression among these groups? What role do social determinants of health play in aging disparities?

Molina-Henry said the findings also highlight the need for better access to Alzheimer's disease pre-screening and screening opportunities in communities across the United States. ATRI's Alzheimer's Prevention Trials Program allows people to take quarterly online cognitive tests that can flag those who may be eligible for future clinical trials, while the institute's AlzMatch program collects blood tests in community settings for the same purpose.

"More than ever—particularly for groups who are underrepresented in research—it's important to participate in screening efforts, to have your blood drawn and if eligible, to join a clinical trial," Molina-Henry said. "Contributing to research in this way adds critical diversity and helps us answer questions about this very devastating disease."

More information: Doris Patricia Molina-Henry et al, Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial, *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.13803

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