Predicting Alzheimer's dementia in oldest of the old

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A new study indicates that severity of amyloid deposition in the brain—not just age—may be key to determining who will benefit from new anti-amyloid therapies to delay the progression of Alzheimer's disease.

University of Pittsburgh clinicians and scientists report that the accumulation of toxic amyloid beta clumps that signal Alzheimer's disease pathology accelerates in old age, but the baseline amyloid burden and the overall brain health going into this acceleration are more powerful predictors of who is most likely to progress to Alzheimer's. The paper is published today in *Neurology*.

"Understanding the complexity of the increased amyloid accumulation, when individuals are cognitively normal, is critical for improved implementation of dementia treatments," said corresponding author Oscar Lopez, M.D., professor of neurology at Pitt and chief of cognitive and behavioral neurology at UPMC.

The presence and the overall quantity and distribution of amyloid beta, or A-beta, clumps in the brain are some of the most common neuropathologies associated with Alzheimer's. Yet, while people who are 80 and older have the highest prevalence of Alzheimer's-associated dementias, most studies that measured A-beta burden in the brain using imaging techniques have focused on younger populations. As such, the connection between A-beta and dementia in the oldest of the old has remained unclear.

Lopez and his colleagues set to change that by examining the relationship between A-beta deposition and new cases of dementia in 94 elderly individuals who were cognitively unimpaired when the study launched. Participants were enrolled in the study at a mean age of 85 and followed for 11 years or until their passing, receiving at least two PET-scans over the course of the study. The rate of amyloid deposition in the brain of these individuals was compared with a younger group from the Australian Imaging, Biomarker, and Lifestyle (AIBL) study.

Researchers observed a steady increase in A-beta accumulation in all participants over time, independent of their A-beta status at the

beginning of the study. But this accumulation was significantly faster in patients in their 80s and older compared to participants in their late 60s, explaining the higher prevalence of A-beta in the oldest of the old.

In the end, very few participants developed dementia without having A-beta deposits in the brain. Importantly, individuals whose brain scans were positive for amyloid at the beginning of the study developed dementia two years earlier than those who were amyloid-negative.

Researchers also found that the short-term change in A-beta alone over a period of 1.8 years could not predict future risk of [dementia](#). By contrast, the severity of baseline A-beta burden, along with other markers of brain damage defined by the presence of white matter lesions (a marker of small vessel disease) and decrease in gray matter thickness in the brain cortex (a marker of neurodegeneration) were the strongest predictors of risk, indicating that an active pathological process was already in place when the study began.

"Our findings are consistent with studies showing that the amyloid accumulation in the brain takes decades to develop, and occurs in the context of other [brain](#) pathologies, specifically small vessel disease," said Lopez, who also directs Pitt's Alzheimer's Disease Research Center. "Whether there is a vascular process that occurs in parallel to the A-beta deposition could not be examined in this study. However, understanding of the timing of the presence of these pathologies will be critical for the implementation of future primary prevention therapies."

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More information: Association Between β-Amyloid Accumulation and Incident Dementia in Individuals 80 Years or Older Without Dementia, *Neurology* (2023). DOI: 10.1212/WNL.0000000000207920. www.neurology.org/doi/10.1212/WNL.0000000000207920

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