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Blood proteins reveal how menopause may shape brain health later in life

Researchers at UC Santa Barbara, UC San Francisco and international collaborators are uncovering the cascade of molecular events that happen when women undergo menopause, a time of life marked by endocrine changes and symptoms like hot flashes, brain fog and sleep disturbances.

“Menopause is not an isolated reproductive event,” said Emily Jacobs, a professor of psychological and brain sciences at UCSB. “It is a whole-body biological transition. Now we can begin to see a molecular fingerprint of that transition in the blood and ask how it relates to brain health decades later.”

In their findings, published in Nature Medicine, Jacobs and colleagues found increases in levels of 16 molecules implicated in brain aging and dementia risk. While the increased presence of these molecules do not directly lead to dementia, Jacobs is careful to point out, they are giving scientists insight into biological processes that start to shift in midlife. These insights open up new avenues for targeted interventions to promote healthy brain aging.

Using advanced proteomic technologies, the researchers examined thousands of proteins in cohorts of pre-, peri- and postmenopausal women from the Jacobs Lab’s Healthy Aging Study, a project launched to investigate brain and cognitive function

in women and men in midlife. They identified a set of proteins that change across the menopause transition, including proteins involved in inflammatory and neuronal processes, as well as molecules associated with Alzheimer's disease. These shifts were more closely related to a woman's menopause stage than her exact age, suggesting that it is menopause – not just aging – that triggered the changes. These results were confirmed in another database of more than 2,800 women from the UK Biobank, which also showed that menopause is tied to molecular signatures of accelerated aging across multiple organ systems.

They then investigated this biological transition's link to brain health, looking at data from four independent cohorts totaling nearly 12,000 older women. They found that women who harbored higher levels of these "risk" proteins were more likely to show poorer cognitive outcomes and, in the largest cohort, the signature was associated with a modestly greater risk of developing Alzheimer's dementia over the following 16 years.

The team's goal is to develop a blood test that can act as an early-warning sign of dementia risk — the same way cholesterol tests are used to gauge heart disease risk. This could let clinicians identify people who, in midlife, might benefit from early interventions.

"Midlife is a critical window for both men and women where we can really set up the brain to be more resilient or more vulnerable to dementia in later life," said study senior author Kaitlin Casaletto. "For women, menopause may be this especially powerful time to intervene."

"The findings do not mean that menopause causes Alzheimer's disease," Casaletto is careful to point out. Most women do not develop Alzheimer's, she said, and the clinical significance of individual Alzheimer's-related protein changes detected during midlife remains uncertain. Rather, the study highlights the importance of menopause as an opportunity to study brain aging — and eventually identify factors that promote both risk and resilience.

"Women spend roughly one third of their lives after the menopause transition, yet we know remarkably little about the biology connecting menopause to later-life brain health," Jacobs said. "These findings give us a new foothold for asking that question and ultimately for identifying who may benefit most from intervention during this critical window."

The authors note that longitudinal studies following the same women across the menopause transition will be essential to determine how changes in hormones, proteins, symptoms and brain health unfold together over time. UCSB's team, in collaboration with scientists from around the country, is now launching the Longitudinal Menopause Project to do just that, and they are actively recruiting researchers.

The study was led by Madeline Wood Alexander at Sunnybrook Research Institute in Canada and Rowan Saloner and Kaitlin Casaletto at UCSF, with collaborators from UCSB, UCSF, Stanford University, the University of Toronto and other institutions. The work was supported in part by the Ann S. Bowers Women's Brain Health Initiative, Wellcome Leap, the National Institutes of Health and the Noyce Trust.

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