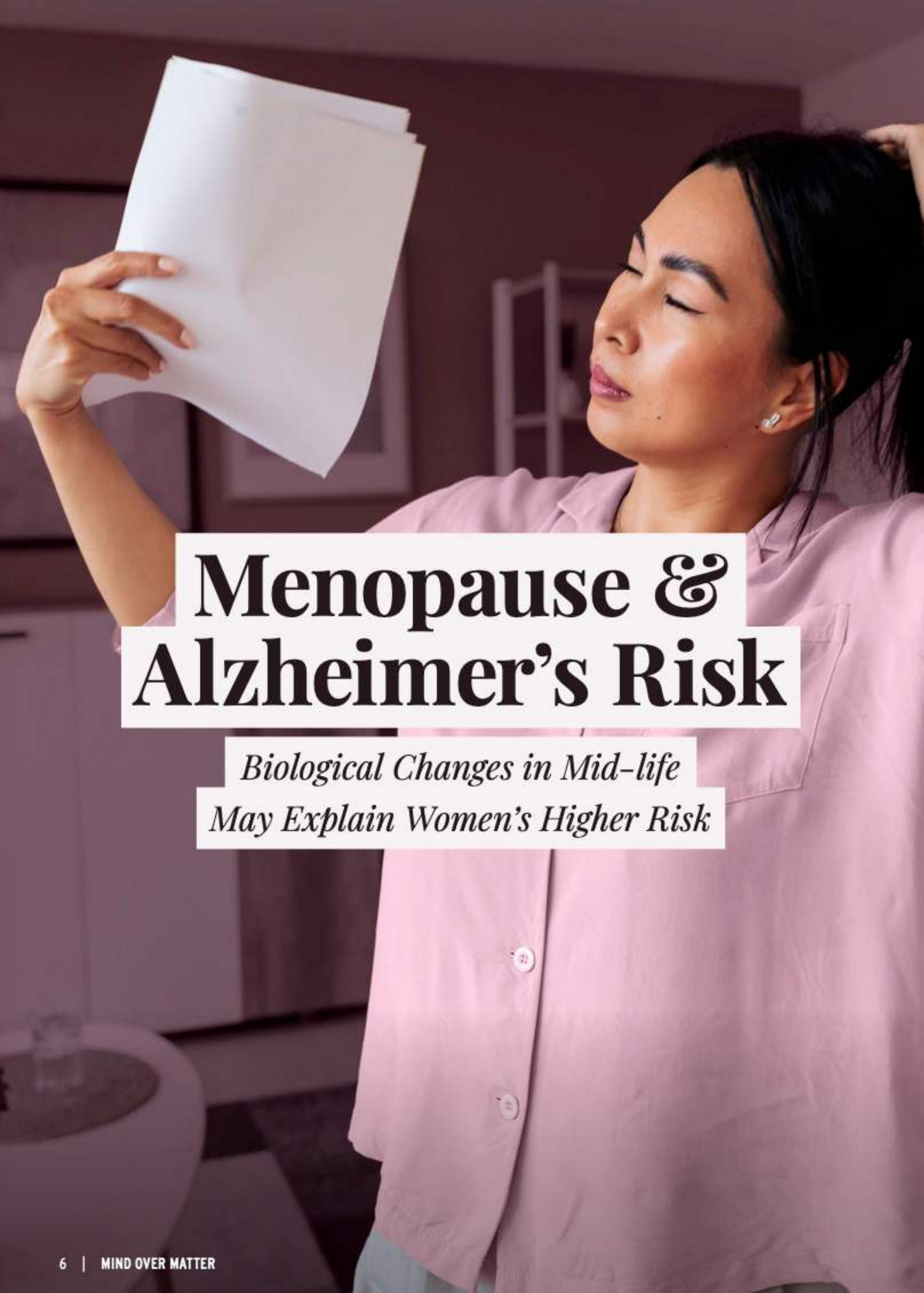


Menopause & Alzheimer's Risk

Biological Changes in Mid-life May Explain Women's Higher Risk



About two-thirds of people living with Alzheimer's disease (AD) are women, a sex-related difference that cannot be fully explained by women's longer lifespan.

While AD typically affects people after the age of 65, its disease processes can begin one to two decades earlier, long before symptoms surface. In women, that timeframe overlaps with menopause.

In a previous issue of Mind Over Matter®, we shared evidence on the significant brain alterations that occur in concert with the loss of estrogen during menopause, hot flashes, and night sweats, and their links to brain health. We also discussed whether menopause hormone therapy (MHT), which typically involves some form of estrogen, may provide brain benefits and reduce dementia risk.

For this article, we spoke to leading researchers who are investigating additional biological changes that take place during the menopausal transition to see whether they may explain why women have a higher risk of developing AD in later life.

The latest research avenues – the interaction between estrogen loss and the *APOE* genotype, protein signatures in the blood, and sex-related differences in tau tangles – have revealed some compelling insights.

MENOPAUSE BRAIN IS REAL: PREVIOUS EVIDENCE

Two years ago, we shared groundbreaking evidence from brain imaging studies of women in mid-life in the article *Menopause Brain is Real* in Mind Over Matter volume 19.

Work by Dr. Lisa Mosconi and Dr. Roberta Diaz Brinton identified brain changes that overlapped with the loss of estrogen during menopause. They found:

- **inefficient mitochondrial activity** in the same brain regions as occurs in people with AD;
- **decreased glucose metabolism in the temporal lobes,** which play a role in memory and perception;
- **lower white matter volume;**
- **the presence of amyloid,** with higher amounts in women with the *APOEe4* genotype; and
- an **increased density in estrogen receptors** was associated with memory lapses, mood swings, and lower cognitive test scores in postmenopausal women.

Dr. Mosconi is Founder and Director of the Weill Cornell Women's Brain Initiative and Alzheimer's Prevention Program

at Weill Cornell Medicine and New York-Presbyterian. She is also Program Director of the Wellcome Leap CARE (Cutting Alzheimer's Risk through Endocrinology), a $50-million program aiming to cut the lifetime risk of AD in women in half by 2050.

Dr. Brinton is Director of the University of Arizona Health Sciences Center for Innovation in Brain Science and one of 27 principal investigators of the Wellcome Leap CARE program.

Dr. Pauline Maki and Dr. Rebecca Thurston's MsBrain study provided **new insights on how hot flashes and night sweats affect the brain:**

- **hot flashes** are associated with changes in brain areas involved in memory;
- women who experience more **night sweats** have more white matter hyperintensities (WHIs) in their brains than those with fewer night sweats; and
- having more **night sweats** during sleep is significantly associated with lower levels of amyloid in blood, indicating more amyloid in the brain, a known AD risk factor.

Dr. Maki is Director of the Women's Mental Health Research Program and Senior Director of Research at the Center for Research on Women and Gender at the University of Illinois, Chicago and a member of Women's Brain Health Initiative's expert panel. Dr. Thurston is the Pittsburgh Foundation Chair in Women's Health and Dementia at the University of Pittsburgh and a principal investigator for the Wellcome Leap CARE program.

MHT is not recommended at any age to treat or prevent a decline in cognitive function or dementia, due to a lack of conclusive evidence.

Read the full story at **wbhi.org/menopause-brain**.

ESTROGEN LOSS & *APOEe4* INTERACTION

The three biggest factors for late-onset AD are age, being female, and the *APOEe4* gene variant. The combination of being female and carrying *APOEe4* confers the highest risk.

Everyone inherits two copies of the *APOE* gene, which plays an essential role in lipid metabolism and other brain cell functions. There are three common variations or genotypes: *APOEe2* is relatively rare and known to be protective, and *APOEe3*, the most common, is neutral.

APOEe4, the strongest genetic risk factor for AD, is associated with neuroinflammation, increased deposition and impaired clearance of amyloid, and faster tau buildup.

Dr. Christian Pike, the Kevin Xu Chair in Gerontology and Assistant Dean of Research at the University of Southern California Leonard Davis School of Gerontology, studies how the significant loss of estrogen during menopause and *APOE* genotype interact and influence AD risk in women.

> **ESTROGEN PERFORMS MANY FUNCTIONS IN THE BRAIN, INCLUDING SUPPORTING ENERGY METABOLISM AND NEURON GROWTH AND SURVIVAL, CLEARING TOXIC AMYLOID, AND REDUCING INFLAMMATION.**

He and his colleagues reviewed human and animal studies for clues about the role of estrogen in AD risk and whether *APOE* status has an impact. In their paper, published in *Journal of Neuroendocrinology* in November 2022, they found that *APOEe4* appears to modify how the brain and body respond to MHT. The findings were interesting yet mixed:

- **MHT reduced amyloid buildup and lowered dementia risk in *APOEe4* carriers**, but for non-carriers, MHT was associated with better memory and verbal fluency; and
- in the body, **MHT showed benefits in addressing adverse cholesterol changes,** but appeared to work better in *APOEe4* non-carriers than in carriers.

> **WHETHER HORMONE THERAPY MAY BE BENEFICIAL FOR BRAIN HEALTH IS AFFECTED BY MULTIPLE VARIABLES, INCLUDING THE TYPE OF ESTROGEN AND TREATMENT TIMING.**

Dr. Pike, continued: "An interesting hypothesis that emerged from our study is that the *APOE* genotype changes the responsiveness of estrogen receptors in the brain, suggesting that *APOE* status should be included in a personalized care approach to MHT."

Dr. Pike is currently working with a pharmaceutical company to develop a bioidentical MHT that targets specific estrogen receptors and accounts for *APOE* status.

PROTEIN CHANGES IN BLOOD DURING MENOPAUSE REVEAL AD RISK FACTORS

Proteins are the building blocks of all biological processes. Advances in technology now allow scientists to study up to thousands of proteins in a single blood sample. These "proteomics" studies capture real-time changes at the molecular level.

Dr. Kaitlin Casaletto has been leading groundbreaking proteomics studies to look for protein differences that arise during menopause. She is an associate professor and researcher at

the University of California, San Francisco, Weill Institute for Neurosciences and a clinical neuropsychologist who sees patients at the UCSF Edward and Pearl Fein Memory and Aging Center. She is also a principal investigator for the Wellcome Leap CARE program.

In one study, Dr. Casaletto and colleagues analyzed biological changes in 120 blood proteins and their links to brain aging using data from multiple studies. First, using data from about 100 healthy women aged 43 to 58 who were not taking MHT and were carefully grouped by menopausal status, the investigators identified 16 proteins that were elevated in postmenopausal compared with premenopausal women.

These proteins were related to inflammation, brain and nerve signalling, and metabolic and AD processes. Notably, this "menopause protein signature" tracked with hormonal shifts, not chronological age.

WOMEN WITH VASOMOTOR SYMPTOMS HAD THE MOST DRAMATIC INCREASES IN INFLAMMATORY MENOPAUSE PROTEINS.

Night sweats were associated with higher menopause protein signature scores, whereas vaginal dryness was associated with lower scores. The study found no associations between daytime hot flashes or irritability and menopause protein signature.

Next, Dr. Casaletto and her team evaluated how the menopause protein signature related to cognitive outcomes in later life using data from four other studies of older women who were ten years or more post menopause.

THEY FOUND THAT WOMEN WITH HIGHER MENOPAUSE PROTEIN SIGNATURES HAD FASTER COGNITIVE DECLINE AND HIGHER LEVELS OF ONE AD MARKER IN PARTICULAR, A FORM OF TAU CALLED P-TAU231.

"P-tau231 is a good marker for AD because it measures amyloid-related tau. It was pretty remarkable to find that in clinically normal older women, higher p-tau231 decades after menopause was still significantly associated with an earlier menopause," Dr. Casaletto explained.

"Note that although postmenopausal women showed elevated p-tau231 compared to premenopausal women, their levels were not higher than those found in age-matched men."

A preprint of the study was published on medRxiv in February 2026. The investigators have submitted it to a peer-reviewed journal and are awaiting acceptance for publication.

In a second study, Dr. Casaletto and her team investigated whether the timing of menopause is associated with protein changes in older women, and whether this might reveal insights into dementia risk.

They analyzed data from the U.K. Biobank for more than 15,000 women who were about ten years post menopause and then replicated their findings with independent data from more than 1,200 similar women who had participated in the Women's Health Initiative Long Life Study.

THE RESEARCHERS FOUND THAT WOMEN WHO EXPERIENCED MENOPAUSE AT AN EARLIER AGE HAD HIGHER LEVELS OF PROTEINS ASSOCIATED WITH INFLAMMATION, TISSUE BREAKDOWN, AND CELL DEATH.

On the other hand, later menopause was associated with increases in proteins involved in bone maintenance, lipid transport, and growth factor signalling.

Next, they estimated the biological age of various organs based on the protein signatures. Earlier menopause tracked with an older biological age, and later menopause was associated with a younger biological age across multiple organ systems. Importantly, menopause timing proteins predicted future cognitive and brain structural outcomes and dementia risk: women with higher signatures had a higher risk.

"Earlier menopause was associated with accelerated aging in most of the organs we studied, including the brain, heart, liver, lungs, and immune system. In particular, the menopause protein signature tracked with brain aging and specifically with the age of oligodendrocytes, which are helper brain cells that produce the fatty sheaths that promote fast communication across neurons," said Dr. Casaletto.

A preprint of the study was published on medRxiv in April 2026. The investigators have submitted the paper to a peer-reviewed journal and are awaiting acceptance for publication.

"Overall, our findings confirm that the age of menopause is a biologically meaningful marker for determining women's health and future brain health risk. As a clinician, the age of menopause is a helpful indicator of a woman's biological age, beyond chronological age, for understanding their health risks," said Dr. Casaletto.

SEX-RELATED DIFFERENCES IN TAU BUILDUP

In the late 2010s, studies of post-mortem tissue reported that tau accumulation was higher in older women compared to older men. The news inspired Dr. Rachel Buckley to learn more, especially for women in the 50 to 70 age group.

She is an investigator at the Mass General Research Institute, an associate professor of neurology at Mass General Brigham and Harvard Medical School, and a principal investigator for the Wellcome Leap CARE program.

"The sex difference in tau was striking, especially as it was more pronounced in brain areas affected early in AD processes," said Dr. Buckley.

Tau data from positron emission tomography (PET) has only become available in the past five years. For their first study, Dr. Buckley and her team analyzed sex differences in tau-PET data from six major studies that followed almost 1,400 people without dementia for an average of about three years.

THEY FOUND THAT WOMEN WITH HIGH AMYLOID LEVELS ACCUMULATED TAU TANGLES SIGNIFICANTLY FASTER THAN MEN WITH HIGH AMYLOID, PARTICULARLY IN MEMORY- AND VISION-RELATED BRAIN AREAS. BY CONTRAST, WOMEN AND MEN WITH LOW AMYLOID HAD ALMOST NO TAU ACCUMULATION.

"We think that once amyloid plaques begin, they ignite AD processes, and women's brains react more aggressively, building up tau more quickly than men's brains," said Dr. Buckley.

Additionally, she and her team found that women carriers of the *APOEe4* variant showed faster tau buildup than male *APOEe4* carriers. The study was published in *JAMA Neurology* in March 2025.

"Our results show there are real biological differences taking place in mid-life, confirming that women's higher AD rates are not just due to a longer lifespan," said Dr. Buckley. "This matters because if women with AD have more tau, they may not qualify for clinical trials of new treatments unless eligibility criteria are adjusted to account for sex-specific differences."

The next question Dr. Buckley and her colleague Dr. Gillian Coughlan sought to answer was whether higher tau accumulation in women negatively affects memory and cognitive function over time.

For their meta-analysis published in *Alzheimer's & Dementia* in February 2026, they analyzed tau-PET, amyloid-PET, *APOEe4*, and cognitive performance data from 1,007 cognitively healthy adults who were followed for an average of almost nine years within the A4/LEARN clinical trial, the Harvard Aging Brain Study (HABS), and the Wisconsin Registry for Alzheimer's Prevention (WRAP).

The results were surprising:

- at lower levels of tau, **women outperformed men on cognitive tests,** especially on memory tasks;
- **as tau levels rose, the cognitive advantage for women disappeared,** and they showed a faster rate of cognitive decline than men; and
- **the difference in tau accumulation was higher for women in brain regions affected by AD.** Notably, amyloid levels and *APOEe4* status did not explain the differences.

In a separate study, Dr. Buckley and Dr. Coughlan analyzed HABS PET data collected over about five years to test the extent to which MHT use is associated with later-life amyloid and tau accumulation. They compared results for 146 women ages 51 to 89, split evenly into two age-matched groups: half had used MHT and half had not.

Interestingly, older women (over 70) who used MHT showed faster tau accumulation in memory-related brain regions compared to non-MHT users. By contrast, there was little difference in tau accumulation between MHT users and non-users among younger women (under 70).

The study was published in March 2025 in *Science Advances*. The authors noted that older women who took MHT likely did so before the landmark Women's Health Initiative study published in 2002 that found combined estrogen and progestin increased the risks of breast cancer, stroke, and blood clots.

> ***We must also keep in mind that our study was observational, so the question of whether MHT causes faster tau accumulation remains inconclusive.***

Dr. Buckley continued: "However, our findings aligned with the 'window of opportunity' hypothesis: there may be brain health benefits when MHT is initiated soon after menopause symptoms arise but may be harmful if taken much later."

In conclusion, these exciting new frontiers of investigation point to a future in which novel biomarkers may assist in an earlier identification of AD risk in women around the menopausal transition and inform a more personalized approach to menopause care, including determining whether and when MHT might be beneficial for brain health.