

A woman with short brown hair, wearing a green and white striped shirt, is shown in profile from the chest up. She is holding a clear plastic ice cube tray in her left hand and using her right hand to bring an ice cube to her mouth. The background is a soft, out-of-focus teal color.

# Menopause Brain is Real

**BRAIN CHANGES DURING MENOPAUSE**

**MAY AFFECT BRAIN HEALTH**

Some women sail through menopause with no symptoms, while others experience wonky periods, unwanted weight gain, and hot flashes.

Menopause can also affect the brain. About 40 to 60% of women have cognitive complaints, including forgetfulness, insomnia, mood swings, and brain fog. Some research suggests women's brains undergo significant alterations in structure, energy metabolism, and memory circuitry during menopause - changes that do not occur in men of the same ages.

These changes have been linked with challenging neurological symptoms women actually feel, according to Dr. Lisa Mosconi, Director of the Weill Cornell Women's Brain Initiative and Alzheimer's Prevention Program at Weill Cornell Medicine and NewYork Presbyterian in New York City and author of the book *The Menopause Brain*.

**“Menopause is like a customized operating system update for the brain. This isn't just a metaphor – it reflects the neurobiological changes that prepare women's brains for the next non-reproductive phase of their lives.**

Mind Over Matter® rounded up the latest evidence and spoke to leading researchers about brain changes that take place during menopause and how they may affect brain health.

This article also discusses whether current treatments for hot flashes have cognitive benefits and two different treatment strategies under investigation for reducing hot flashes that may help address memory issues and potentially lower the risk of Alzheimer's disease (AD).

## LOWER ESTROGEN & BRAIN CHANGES

Dr. Jill Goldstein and colleagues at Brigham and Women's Hospital and Harvard Medical School conducted some of the earliest human brain imaging research on women's brains during midlife. They explored the impact of sex and reproductive status on memory using magnetic resonance imaging (MRI).

In their study published in *The Journal of Neuroscience* in 2016, they found that lower estrogen levels in women were related to more pronounced changes in connectivity in the hippocampus

- the brain area responsible for memory and learning - and poorer performance on a memory retrieval task.

They also found some good news: a subgroup of postmenopausal women with high memory performance showed similar brain activity as premenopausal women.

Other researchers have been exploring brain energy changes during menopause. “Before the menopausal transition, estrogen activates the brain's energy system, promoting glucose uptake and its conversion into energy. It also keeps the brain dependent on glucose as its primary fuel,” explained Dr. Roberta Brinton, Director of the University of Arizona Health Sciences Center for Innovation in Brain Science and Regents professor of pharmacology at the University of Arizona College of Medicine - Tucson.

**“WHEN ESTROGEN DROPS DURING MENOPAUSE, THE BRAIN IS THE FIRST ORGAN AFFECTED. THE LOSS SETS OFF A STARVATION RESPONSE, REQUIRING THE BRAIN TO REWIRE AND FIND NEW FUEL SOURCES.**

More than two decades ago, Dr. Brinton discovered that when estrogen levels decreased in mice during menopause, energy-producing structures inside brain cells called mitochondria became inefficient and made heat instead of energy. She was surprised to observe that the mitochondria in menopausal mice looked more like mitochondria in mouse models of AD than in normal mice. →

## MENOPAUSE FAST FACTS

- 100% of women experience menopause;
- menopause is a transition that occurs between the ages of 45 and 55. You are in menopause if it has been 12 months or more since your last period;
- three out of four women experience menopause symptoms that interfere with daily life;
- up to 80% of women experience hot flashes during the menopausal transition and well into postmenopause, lasting about seven to ten years, or more; and
- each hot flash lasts 30 seconds to ten minutes.

## WORKPLACE SUPPORT FOR WOMEN EXPERIENCING MENOPAUSE

Employers lose out when a large portion of women – 17% between the ages of 50 and 64 in the United States – quit or consider quitting their jobs due to a lack of support for menopause symptoms, according to a recent article in *Forbes*.

Savvy employers recognize supporting women through menopause confers the following competitive advantages:

- › reduces absenteeism;
- › helps women advance into leadership positions;
- › boosts recruitment and talent retention;
- › improves the company's brand image;
- › reduces the risk of discrimination claims; and
- › improves productivity, job satisfaction, workplace culture, and gender equality.

Read more at <https://www.forbes.com/sites/michelletravis/2024/06/04/the-business-case-for-supporting-employees-through-menopause/>

“Breaking the silence and the stigma of menopause at work isn't just the right thing to do, it also benefits the bottom line,” according to “Menopause and Work in Canada”, a new report by the Menopause Foundation of Canada.

The organization also provides an informative resource for employers under its Menopause Works Here campaign called *Creating a Menopause Inclusive Workplace: A Playbook for Employers*. Learn more at [menopausefoundationcanada.ca](http://menopausefoundationcanada.ca).

To see if these same changes occur in women, she collaborated with Dr. Mosconi to analyze the first positron emission tomography (PET) scans of women's brains before and after menopause. They observed similar changes – a loss of brain energy and inefficient mitochondrial activity in the same brain regions as occurs in individuals with AD.

The changes were most pronounced in the postmenopausal group, somewhat present in the perimenopausal group, and lowest in the premenopausal group.

Drs. Brinton and Mosconi hypothesized that reduced brain energy during menopause might explain why women have an increased risk of developing AD compared to men.

Their paper was published in *PLOS ONE* in 2017.

In a subsequent imaging study published in *Scientific Reports* in 2021, Drs. Mosconi and Brinton found substantial changes in energy metabolism and brain structure in women's brains across all stages of the menopause transition – changes they did not observe in the brains of age-matched men.

The brain scans of 74 postmenopausal women showed the following differences compared to brain scans of 30 premenopausal women:

- › lower white matter volume;
- › decreased glucose metabolism in the temporal lobes, which play a role in memory and perception; and
- › the presence of amyloid beta plaque deposits, with higher amounts seen in women with the *APOE-e4* gene, a genetic risk factor for AD.

**THE BRAINS OF SOME POSTMENOPAUSAL WOMEN, HOWEVER, SHOWED SIGNS OF COMPENSATION, SUCH AS INCREASED CEREBRAL BLOOD FLOW AND ENERGY UTILIZATION IN SOME OF THE SAME AREAS WHERE GLUCOSE USAGE AND BRAIN VOLUME CHANGED.**

Note that it's unclear whether these findings will apply to all women since 42% of the study participants were *APOE-e4* positive, much higher than the 15 to 25% of the general population with this form of the gene.

Most recently, Drs. Mosconi and Brinton discovered the density of estrogen receptors in women's brains increases significantly over the menopause transition. They observed that this increase was associated with memory lapses, mood swings, and lower scores on some cognitive tests in postmenopausal women.

“The increase in receptors is likely an ineffective compensatory response to the loss of estrogen that may result in these cognitive changes,” Dr. Brinton said.

This first-ever estrogen brain imaging study assessed 54 women, divided into three groups of 18 premenopausal,

perimenopausal, and postmenopausal individuals. The findings were published in *Scientific Reports* in June 2024.

## HOT FLASHES & NIGHT SWEATS

Another brain change that occurs during menopause causes hot flashes. These bothersome “personal summers” begin in specific neurons in the hypothalamus, the control centre in the brain that regulates hormone production and body temperature.

The KNDy (“candy”) neurons – so-called because they produce little proteins called kisspeptin, neurokinin B, and dynorphin – become larger and fire inappropriately. This stimulates other neurons in the hypothalamus to tell the body to get rid of heat. As a result, blood moves to the skin’s surface, and sweat glands release sweat.

Dr. Pauline Maki, another leading menopause research pioneer, began investigating women’s brain health and menopause over two decades ago at the National Institutes of Health (NIH). She is now 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. Maki also leads the largest longitudinal study of brain changes across the menopause transition as part of the NIH-funded Adult Aging Brain Connectome Project. She first reported an association between hot flashes and memory function more than 15 years ago.

Dr. Maki found that more frequent hot flashes were associated with worse memory for words.

It’s important to note that her study used skin sensors to measure hot flashes and night sweats. “Women underreport night sweats on average by about 40% because they’re not awake enough to realize they’re happening or they’re too busy trying to get back to sleep to record their data,” she said.

In a subsequent neuroimaging study, Dr. Maki showed that hot flashes were associated with alterations in brain areas involved in memory. To further that work, she began a collaboration with Dr. Rebecca Thurston, Pittsburgh Foundation Chair in Women’s Health and Dementia and professor of psychiatry, clinical and translational science, epidemiology, and psychology at the University of Pittsburgh, to conduct MsBrain, an NIH-funded longitudinal neuroimaging study. The MsBrain study has revealed some compelling insights.

Drs. Maki and Thurston found that women ages 45 to 67 who experienced more night sweats had more white matter hyper-

intensities (WMHs) in their brains, as seen on MRI, than women with fewer night sweats.

These results were published in *Neurology* in January 2023.

WMHs are small areas of damage in the brain’s white matter commonly seen in brain scans of older individuals. However, an increased number of WMHs is associated with cognitive impairment, dementia, AD, and cerebrovascular disease caused by high blood pressure.

In a second study, Drs. Maki and Thurston discovered that having more night sweats during sleep was significantly associated with lower levels of amyloid beta in blood samples of women in late perimenopause or postmenopause. Lower amyloid beta in blood indicates more amyloid beta in the brain, a known AD risk factor. Their study was published in *American Journal of Obstetrics and Gynecology* in March 2024.

**“ IT MAKES SENSE THAT NIGHT SWEATS AND THE RESULTING SLEEP DISRUPTION COULD AFFECT MEMORY AND ALZHEIMER’S DISEASE BIOMARKERS BECAUSE WE KNOW THAT SLEEP IS ESSENTIAL FOR SWEEPING OUT EXCESS AMYLOID BETA IN THE BRAIN.**

“However, we don’t know if the associations we discovered are causal. We hope our longer-term research underway will answer the question,” Dr. Maki continued.

As their MsBrain study continues, Drs. Maki and Thurston are examining associations between night sweats and sleep disruptions with increases in WMHs and amyloid beta over ten years. They are using skin monitors to measure sleep quality and night sweats, MRI brain imaging to examine mitochondrial function, and conducting neuropsychological testing.

## WILL TREATING HOT FLASHES IMPROVE BRAIN HEALTH?

There are several therapies available for treating hot flashes, including estrogen therapy, nonhormonal drugs, and alternative therapies. Estrogen therapy, for example, can effectively reduce the frequency and severity of hot flashes by 75%.

However, none of the treatments for hot flashes available today can accurately claim they provide cognitive benefits or prevent AD because there is no supporting evidence yet from randomized controlled trials, Dr. Maki advised.

“Four large, randomized controlled trials failed to find cognitive benefits associated with estrogen therapy for →

women in menopause,” said Dr. Maki. “However, all of these studies included women with minimal symptoms.”

**“Whether estrogen therapy can improve cognition in menopausal women with hot flashes and other symptoms remains an open question.”**

The North American Menopause Society issued a position statement in 2022 on the use of hormone therapy. Co-authored by Dr. Maki and Dr. Thurston, it says, “In the absence of more definitive findings, hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia.” It also says there is a small, elevated dementia risk for women over 65 who begin hormone therapy.

## RESEARCHING NEW TREATMENT STRATEGIES

Menopause researchers are investigating different nonhormonal treatment strategies for reducing hot flashes and potentially improving brain health.

Drs. Brinton and Mosconi are conducting a Phase 2 clinical study of PhytoSERM, an oral supplement containing three plant-based phytoestrogens called genistein, daidzein, and S-equol. These ingredients were selected for their ability to promote estrogen action in the brain but not breast tissue, addressing concerns regarding breast cancer risk associated with hormonal estrogen therapy, Dr. Brinton said.

**“ESTROGEN THERAPY SUSTAINS THE UTILIZATION OF GLUCOSE IN THE BRAIN AND PREVENTS THE UTILIZATION OF OTHER FUELS. OUR DATA FROM PRECLINICAL STUDIES SUGGESTS PHYTOSERM WILL BEHAVE SIMILARLY TO PROMOTE BRAIN HEALTH WHILE ALSO PROTECTING BREAST HEALTH.”**

The study is recruiting women ages 45 to 60 in perimenopause or postmenopause who are experiencing hot flashes. Dr. Brinton’s team will evaluate whether PhytoSERM reduces hot flashes, measured by skin sensors, and improves sleep quality and cognitive test scores for working memory, episodic memory, verbal learning, and cognitive processing speed, compared to a placebo.

Dr. Mosconi’s team will assess PET brain scans to see if PhytoSERM improves glucose metabolism. They will also

analyze amyloid beta as a marker of AD risk and other markers of neuroinflammation and neurodegeneration.

Dr. Maki, on the other hand, is planning to investigate an entirely different nonhormonal treatment strategy. “Most research to date has focused on decreased estrogen at menopause as a key factor contributing to cognitive and brain aging in women,” she said.

**“BUT HOT FLASHES AND NIGHT SWEATS PERSIST FOR MANY YEARS BEYOND THE FINAL MENSTRUAL PERIOD, AFTER ESTROGEN LEVELS HAVE PLATEAUED AND INTO DEMENTIA DIAGNOSIS TIME FRAMES. I HYPOTHEZIZE IT’S THE PERSISTENT NIGHT SWEATS CAUSING BRAIN HEALTH ISSUES, NOT THE WITHDRAWAL FROM ESTROGEN.”**

Dr. Maki said targeting hot flashes and night sweats directly is a promising approach. In a previous clinical study, she found that memory improved when hot flashes were treated with the nonhormonal therapy stellate ganglion blockade, an anesthetic injected into a nerve bundle in the neck.

“Stellate ganglion blockade reduced 75% of moderate to severe hot flashes, and memory bounced back in proportion to the therapeutic response, supporting my hypothesis,” Dr. Maki said. “We are planning more trials with new nonhormonal interventions to directly treat hot flashes and night sweats.”

## HOW TO NAVIGATE BRAIN HEALTH CHALLENGES DURING MENOPAUSE

Until we have solid evidence that estrogen therapy or treating hot flashes and night sweats will improve cognitive health and reduce AD risk in menopausal women, it’s essential to incorporate Women’s Brain Health Initiative’s Six Pillars of Brain Health into your daily life – eat a healthy diet, get regular exercise, improve your sleep habits, enjoy social activities, reduce stress, and engage in cognitively challenging activities.

“If we bring healthier brains and a higher cognitive reserve into menopause, we’re going to be more resilient to developing Alzheimer’s disease later,” said Dr. Maki.

If you are concerned about menopause symptoms, speak to your doctor or a Menopause Practitioner. The Menopause Society provides an online search tool for finding practitioners in the United States, Canada, and other countries at [portal.menopause.org/NAMS/NAMS/Directory/Menopause-Practitioner.aspx](https://portal.menopause.org/NAMS/NAMS/Directory/Menopause-Practitioner.aspx) 