The Neuroprotective Role of Estrogen Across Reproductive Stages and Its Implications for Alzheimer's Disease in Women

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Abstract

Hormonal changes across lifespan (stages) in women could be contributing, where estrogen and prog levels fluctuate. Estrogen has been shown to support memory and brain function, so in these stages where estrogen levels decline, it could contribute to AD symptoms, including decline in memory and cognitive function. One key area where estrogen is neuroprotective is through support of memory, communication between nerve cells synapses, and glucose metabolism as well as being an anti-inflammatory agent in the brain. As estrogen levels decline during menopause, regions in the brain like the hippocampus could be more prone to the various symptoms resulting from AD like memory loss, brain fog, and development of amyloid plaques and tau tangles in the brain. Hormone Replacement Therapy (HRT/ERT) has been studied for its role to potentially prevent AD, but results from research have been inconsistent with no proper conclusion.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that slowly destroys cognitive function such as memory, critical thinking skills, and the ability to carry out basic tasks. AD is common in the older population and can begin as many as 10 to 20 years before symptoms such as dementia can occur (Ballard et al., 2011). Many factors contribute to the prevalence and progression of AD such as sudden cognition, genetics, age, metabolic health, lifestyle, and environment.

Recent studies have begun to examine sex-based differences in the context of AD, as two-thirds of clinically diagnosed cases of dementia and AD are women (Barth et al., 2025). This increased risk may be partly attributable to biological factors unique to women. Notably, women undergo specific hormonal phases during their lifetime, including perimenopause, menopause, and post-menopause that change across the reproductive lifespan (Briceno Silva et al., 2024). A primary hormone in the female reproductive system, estrogen, has a broad effect in both the brain, heart, and has been implicated in a number of diseases including cardiovascular and neurodegenerative diseases. Because of women's increased risk of developing Alzheimer's disease, understanding the effect of hormonal changes over time is essential for much-needed research to generate accurate therapies for preventing or treating AD.

Women's Reproductive Stages

Typically, women experience reproductive and hormonal changes throughout their lifetime through three main stages:, peri-menopause, menopause, and post-menopause (McCarthy & Raval, 2020)). Levels of female sex hormones including estrogen and progesterone fluctuate during these periods. Estrogen, the primary female sex hormone made by the ovaries, is responsible for the development of female sex characteristics during puberty and a key regulator of menstrual cycles. Estrogen also supports brain function (Rehbein et al.,

2021). Alternatively, progesterone primarily prepares the body for pregnancy through mediating the ovulatory cycle.

The first stage, peri-menopause, is the transition period that leads up to menopause, typically progressing across age starting from late 30s to early 50s (Briceno Silva et al., 2024). From an evolutionary perspective, this is the point at which there is a tradeoff between reproductive success and survival, leading to fluctuation in hormonal levels due to imbalanced energy homeostasis. One example includes variance in levels of follicle-stimulating hormone (FSH), which regulates reproduction, rises due to decreased ovarian functions and ovarian function declines. This further leads to irregular ovulation and hormone production.

Menopause is the natural end of ovulation, with the average age of occurrence around 51 years old (Briceno Silva et al., 2024). Estrogen and progesterone levels continue to drop significantly, leading to the cessation of ovulation and menstruation. Post-menopause is the stage after a woman has gone through menopause. Some of the hormonal changes that occur are low, stable estrogen levels; FSH levels remain high due to consistently low estrogen; and the ovaries no longer produce significant amounts of hormones. The age that this usually occurs is in the 50s and older.

Hormonal fluctuations have implications in other biological functions across other organs in addition to regulation of the menstrual cycle. When energy homeostasis is imbalanced due to fluctuating hormone levels, include changes in body weight and metabolism. Additionally, disruption of hormone levels across phases, including but not limited to estrogen, therefore contributes to aberrant regulation of hormones in the brain. For example, estrogen is a main factor in maintaining cognitive health by influencing glucose metabolism, neuronal plasticity, oxidative stress, and inflammation (Briceno Silva et al., 2024). It can lead to metabolic dysfunction underlying the pathogenesis of a variety of diseases including those not typically associated with sex including diseases such as Alzheimer's Disease (Camon et al., 2024). Disruption of health-associated hormonal regulation within the CNS provides an opportunity to evaluate the roles of hormonal fluctuations to further understand underlying mechanisms driving the pathogenesis and progression of diseases such as AD.

The functional role of estrogen in the brain across reproductive stages.

Estrogen has been shown to support learning and memory processes in the hippocampus by strengthening how neurons connect and communicate. For example, estrogen receptors are found in the hippocampus and play a role in cognitive function such as memory (Joue et al., 2024) (McEwen et al., 2012). Estrogen is a peptide that affects communication between neurons by increasing synapse formation, strengthening synapse communication, and supports neurotransmitters involved in learning and mood. In cases where women have low estrogen levels, like those experiencing peri-menopause, reduced estrogen levels result in reduction of neuronal signaling strength in tandem. This results in behavioral changes that demonstrate impairment of both memory and mood (Caroni et al., 2012).

Estrogen signaling occurs as a result of its interaction with specific estrogen receptors (ERs). The two types of estrogen receptors include ERα and ERβ (Tang et al., 2019). Both receptor subtypes are expressed in many cells and tissues, and they control key physiological functions in various organ systems, such as reproductive, skeletal, cardiovascular and central nervous systems. ERα is present mainly in the mammary gland, uterus, ovaries, bone, male reproductive organs including testes and epididymis, prostate, liver, and adipose tissue. ERβ is found mostly in the prostate, bladder, ovary, colon, immune system, and similarly in the adipose

tissue. ERα and ERβ both have significant roles in the healthy development and function of the ovaries and protection of the cardiovascular system. While they both serve as receptors for estrogen, ERα plays a prominent role on the mammary gland and uterus, preservation of skeletal homeostasis, and the regulation of metabolism while ERβt plays a significant role in estrogen regulation within the central nervous system and the immune system (Paterni et al., 2014). Additionally, each receptor has tissue-specific functions such as in breast tissue and sub-compartments of the prostate and ovary (Paterni et al., 2014). Here, ERα and ERβ activate growth, cell cycle genes, support tissue repair, associated with AD pathology.

Estrogen receptor levels change with age and menopause due to the levels of estrogen dropping during this stage. The decline reduces the activation in ERα and ERβ. Age-associated loss of estrogen production during menopause has been implicated in a higher risk for metabolic diseases and increased mortality. The ovarian reserve, which produces estrogen, usually reduces the production of estrogen which alters menstrual length during perimenopause (Camon et al., 2024). Loss of estrogen signaling increases inflammation, disrupts neurotransmitters, and reduces synapse formation. Brain imaging techniques are useful in measuring the structural and network connectivity effects of APOE ε2, and changes that occur during menopause. The loss of estrogen and estrogen signaling also decreases hippocampal volumes over the menopausal transition (Russell et al., 2019). Verbal memory and processing speed during menopause relies on the hippocampus, and appears to be particularly affected, with studies showing that estrogen enhances synaptic connectivity in this region, supporting memory retention (Garg & Munshi, 2024). This is due to estrogen loss during this time frame. Brain fog is usually reported during menopause which includes memory lapses, difficulty concentrating, and mental fatigue. These symptoms rely on the hippocampus, which appears to be particularly affected during menopause (Garg & Munshi, 2024).

History of HRT

Due to the considerable decline in hormone levels during menopause, hormone replacement therapy (HRT) arose as a way to treat the symptoms associated with menopause. n Additionally, it has provided researchers with a method to study the effect of changing hormone levels such as estrogen on cognitive decline and the risk for developing AD in women. In the early 1900s - 1920s, the clinical conditions associated with menopause were identified as ‘Hormone Deficiency Syndrome’ and as a result of the reduced hormones chronic diseases such as osteoporosis, cardiovascular events, Alzheimer’s disease, and vaginal atrophy became very common (Cagnacci & Venier, 2019). HRT was first discovered and used in the 1960s, with increased popularity in the 1990s. In 1998, the founding of the Women’s Health Initiative (WHI) aimed to evaluate the effect of HRT on the most common causes of death and disability in postmenopausal women, such as cardiovascular disease, cancer, and osteoporosis (Cagnacci & Venier, 2019). They overall found that women with a genetic predisposition to cardiovascular diseases, cancer, and osteoporosis would be more likely to develop these conditions through HRT but HRT also significantly reduced AD in women.

HRT and dementia

Estrogen loss affects multiple brain regions which are also the most vulnerable to AD. These brain regions include the hippocampus, prefrontal cortex, entorhinal cortex, the temporal lobes, and the posterior cingulate cortex.

The Women's Health Initiative (WHIMS) highlights a consistent study about Menopausal Hormone Therapy (MHT), which may reduce the risk for dementia. Midlife MHT users presented a 26% reduced risk of dementia compared to women who started later in life (Mosconi et al., 2025). If HRT or ERT is started years after that "critical window", which is the period of time that will maximize HRTs benefit and minimize risks, it is less likely to be neuroprotective and prevent against AD. The critical windows include the peri-menopause period. During preclinical studies it was shown that ERT had a higher likelihood of neuroprotective in the peri-menopause period (Zhu et al., 2021).

However, results from subsequent studies examining how menopausal hormone replacement therapy (HRT) influences cognition have been inconsistent, with both WHIMS and the Kronos Early Estrogen Prevention Cognitive and Affective Study have not shown benefit for ERT improving aspects of cognition (Snyder et al., 2016). However, these studies suggest that there may be a benefit to taking hormones during midlife due to the potential reduction in the risk of dementia and AD for certain women; but the degree to which it could treat or prevent cognitive decline is not known yet, and more research will continue to be needed.

Sex-based disparities in research, including AD

Most of the diagnosed cases of AD are among women, but sex-specific biological mechanisms are less studied than those in male. This could be a problem for developing effective and individualized treatment methods for women.Investigation of estrogen and HRT provide evidence linking hormonal fluctuations with cognitive decline and substantiate their relevance in dementia and other cognitive impairment. Clinical trials should therefore prioritize women because of these sex-specific biological factors, specifically hormonal changes like estrogen decline when making treatments for Alzheimer's. This is because hormonal changes directly influence AD risk, progression, and treatment response, yet women in clinical trials continue to remain underrepresented in research. Lower amounts of estrogen leads to higher amounts of inflammation, lower neural connections, and more degeneration of cognitive functions. Based on clear sex-differences in the level of estrogen and progesterone, many reports have failed to address sex-specific responses to treatments like HRT and ERT within clinical trials. This makes it crucial to continue to have trials centered around women when trying to work on new and improved treatment for AD.

Conclusion

The hormonal changes that take place at three different stages of menopause result in an overall decrease in estrogen and progesterone, which in turn have an effect on metabolism, brain function, and ultimately increase risk of Alzheimer's disease and associated cognitive disturbances. Estrogen promotes good health of the brain through various mechanisms, such as strengthening neuronal connections, decreasing inflammation, and protecting the brain from Alzheimer's-related tau tangles and amyloid plaques; thus, its decrease due to menopause increases cognitive vulnerability and increases risk of neurodegenerative diseases in women. Hormone replacement therapy began in the 1960s as a means of treating menopause symptoms by compensating for low hormone levels. Researchers can also use it to investigate the role of estrogen in cognitive decline and the increased likelihood of developing Alzheimer's disease in women. Overall, women are particularly vulnerable to Alzheimer's disease because of biological factors, and they are often not represented in clinical research, trials, and

treatment. Due to recent findings about AD in women and all being inconclusive, this helps understand why more clinical trials need to specifically include women.

References

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *The Lancet*, *377*(9770), 1019–1031. https://doi.org/10.1016/S0140-6736(10)61349-9

Barth, C., Galea, L. A., Jacobs, E. G., Lee, B. H., Westlye, L. T., & De Lange, A.-M. G. (2025). Menopausal hormone therapy and the female brain: Leveraging neuroimaging and prescription registry data from the UK Biobank cohort. *eLife*, *13*, RP99538. https://doi.org/10.7554/eLife.99538.3

Briceno Silva, G., Arvelaez Pascucci, J., Karim, H., Kaur, G., Olivas Lerma, R., Mann, A. K., Gnanasekaran, S., & Thomas Garcia, K. D. (2024). Influence of the Onset of Menopause on the Risk of Developing Alzheimer's Disease. *Cureus*. https://doi.org/10.7759/cureus.69124

Cagnacci, A., & Venier, M. (2019). The Controversial History of Hormone Replacement Therapy. *Medicina*, *55*(9), 602. https://doi.org/10.3390/medicina55090602

Camon, C., Garratt, M., & Correa, S. M. (2024). Exploring the effects of estrogen deficiency and aging on organismal homeostasis during menopause. *Nature Aging*, *4*(12), 1731–1744. https://doi.org/10.1038/s43587-024-00767-0

Caroni, P., Donato, F., & Muller, D. (2012). Structural plasticity upon learning: Regulation and functions. *Nature Reviews Neuroscience*, *13*(7), 478–490. https://doi.org/10.1038/nrn3258

Garg, R., & Munshi, A. (2024). Sleep and Brain Function at Menopause. *Journal of Mid-Life Health*, *15*(4), 221–224. https://doi.org/10.4103/jmh.jmh_201_24

Joue, G., Navarro-Schröder, T., Achtzehn, J., Moffat, S., Hennies, N., Fuß, J., Döller, C., Wolbers, T., & Sommer, T. (2024). Effects of estrogen on spatial navigation and memory. *Psychopharmacology*, *241*(5), 1037–1063. https://doi.org/10.1007/s00213-024-06539-3

McCarthy, M., & Raval, A. P. (2020). The peri-menopause in a woman's life: A systemic inflammatory phase that enables later neurodegenerative disease. *Journal of Neuroinflammation*, *17*(1), 317. https://doi.org/10.1186/s12974-020-01998-9

McEwen, B. S., Akama, K. T., Spencer-Segal, J. L., Milner, T. A., & Waters, E. M. (2012). Estrogen effects on the brain: Actions beyond the hypothalamus via novel mechanisms. *Behavioral Neuroscience*, *126*(1), 4–16. https://doi.org/10.1037/a0026708

Mosconi, L., Nerattini, M., Williams, S., & Fink, M. (2025). New Horizons in Menopause, Menopausal Hormone Therapy, and Alzheimer's Disease: Current Insights and Future Directions. *The Journal of Clinical Endocrinology & Metabolism*, *110*(4), 911–921. https://doi.org/10.1210/clinem/dgaf026

Paterni, I., Granchi, C., Katzenellenbogen, J. A., & Minutolo, F. (2014). Estrogen receptors alpha (ERα) and beta (ERβ): Subtype-selective ligands and clinical potential. *Steroids*, *90*, 13–29. https://doi.org/10.1016/j.steroids.2014.06.012

Rehbein, E., Hornung, J., Sundström Poromaa, I., & Derntl, B. (2021). Shaping of the Female Human Brain by Sex Hormones: A Review. *Neuroendocrinology*, *111*(3), 183–206. https://doi.org/10.1159/000507083

Russell, J. K., Jones, C. K., & Newhouse, P. A. (2019). The Role of Estrogen in Brain and Cognitive Aging. *Neurotherapeutics*, *16*(3), 649–665. https://doi.org/10.1007/s13311-019-00766-9

Snyder, H. M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D. B., Espeland, M. A., Gatz, M., Mielke, M. M., Raber, J., Rapp, P. R., Yaffe, K., & Carrillo, M. C. (2016). Sex biology

contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimer's & Dementia*, *12*(11), 1186–1196. https://doi.org/10.1016/j.jalz.2016.08.004

Tang, Z.-R., Zhang, R., Lian, Z.-X., Deng, S.-L., & Yu, K. (2019). Estrogen-Receptor Expression and Function in Female Reproductive Disease. *Cells*, *8*(10), 1123. https://doi.org/10.3390/cells8101123

Zhu, D., Montagne, A., & Zhao, Z. (2021). Alzheimer's pathogenic mechanisms and underlying sex difference. *Cellular and Molecular Life Sciences*, *78*(11), 4907–4920. https://doi.org/10.1007/s00018-021-03830-w