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Menopause and Risk of Cognitive Impairment - A Literature Review

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ABSTRACT

The World Health Organization (WHO) defines menopause as the permanent cessation of menstruation due to a decrease in ovarian activity without physiological or pathological causes. Twelve months of amenorrhea signal menopause. Menopause usually begins around 50 but can occur at 41, 45, or 40. Menopause between 45 and 55 is different from early menopause. Women are more likely to have cardiovascular illness, parkinsonism, melancholy, osteoporosis, hypertension, weight gain, midlife diabetes, cognitive impairments, and dementia, including Alzheimer's disease (AD). When estrogen levels drop prematurely, women are more likely to acquire certain disorders. Experimental and epidemiological studies suggests that female sex hormones have neuroprotective and anti-aging effects over time. According to new research, estrogen protects and promotes the CNS. Working memory, attention, processing speed, and verbal memory are lower in menopausal women. Age-related estrogen may protect cognition. Estrogens improve brain health by regulating neuropeptides, neurotransmitters, and neurosteroid production, affecting cell death, neuronal development, synaptic plasticity, mitochondrial function, antioxidants, immune system modulation, and β-amyloid reduction. Sex hormone prescriptions ease cognitive impairments in early menopause when estradiol and estrogen receptor levels diminish. The selective estrogen receptor modulators tamoxifen and raloxifene interact with ERα, ERβ, and GPR30 to protect the brain.

Keywords: Aging; Cognitive impairment; Estrogen; Menopause

INTRODUCTION

The World Health Organization (WHO) defines menopause as the permanent cessation of menstrual periods caused by ovarian activity. This concept is predicated on the premise that there are no other clinical or physiological causes of menopause. Women's menopause is diagnosed after they have had amenorrhea for twelve months in a row.[1] Although most women experience menopause around the age of 50, it can start as early as age 40 or as late as 41–45 (early menopause). Every woman who reaches the middle of her life will experience menopause, which is a physiological transformation that signifies the end of her ability to have children.[2,3] Furthermore, prior to the age of 45, 11–14% of women experience the onset of menopause at an earlier age. It is estimated that approximately eighty percent of women go through menopause on their own, without the need for any medical intervention, when their ovarian follicular reserve reduces to an exceptionally low

level. The other twenty percent of women experience menopause as a consequence of a surgical removal of the ovaries, an undetermined removal of the uterus, or treatment-induced events, such as chemotherapy or radiation, in which the ovaries are surgically removed or menstruation is abruptly terminated. The symptoms of menopause and the consequences they have on health are intimately tied to one another.[4,5]

Cognitive issues are more prevalent around the time of menopause, which is characterized by a decrease in hormone levels, particularly estrogen, according to the findings of researchers.[6] An increased risk of cardiovascular disease, parkinsonism, depression, osteoporosis, hypertension, weight gain, diabetes in midlife, cognitive difficulties and dementia (including AD), and hypertension is associated with an early drop in estrogen levels in women. Longitudinal neuroprotective and anti-aging benefits of female sex hormones have been suggested by both experimental and epidemiological research.[7,8]

Objective abnormalities in neuropsychological testing and maintained functional independence for daily activities indicate mild cognitive impairment (MCI). An individual's risk of dementia is doubled compared to the general population if they experience subjective cognitive impairments despite normal neuropsychological test results.[9] Dementia preventive techniques might be better developed if our understanding of the neurological processes that precede and initiate early cognitive decline is enhanced. Mild cognitive decline is related with menopause, because estrogen is essential for processing information and neuronal function.[10]

The subject of this essay is the connection between menopause and the possibility of developing cognitive impairment.

MATERIALS & METHODS

Protocol

This review was performed in compliance with the stipulations set forth in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria.

Eligibility Criteria

This literature review on "menopause" and "cognitive impairment" was prepared to analyze the existing research on these two topics. The studies being considered covered these subjects extensively. Each of the following must be met before your work is considered: 1) To be published, articles must be in English and discuss menopause and cognitive impairment. 2) Papers must have been published after 2018, but before this systematic evaluation. Written contributions in these areas will not be considered for the anthology: Editorial letters, non-DOI submissions, article reviews, and analogous contributions to journal publications are allowed.

Search Strategy

The search for studies to be included in the systematic review was carried out from January, 2nd 2025 using the PubMed and SagePub databases by inputting the words: “"menopause" and "cognitive impairment". A literature review and examination of study titles and abstracts led the study author to change the inclusion and exclusion criteria. The study's supplements contain the new criteria. This was done to narrow the problem's scope and identify topics for additional inquiry. After reviewing comparable research, the author reached this conclusion. When generating the systematic review, only studies that met all inclusion criteria were included. Thus, we only considered research proposals that met all conditions. To make the review as thorough as possible. This initiative sought to gather study title, author, publication date, study location, research study design, and research parameters.

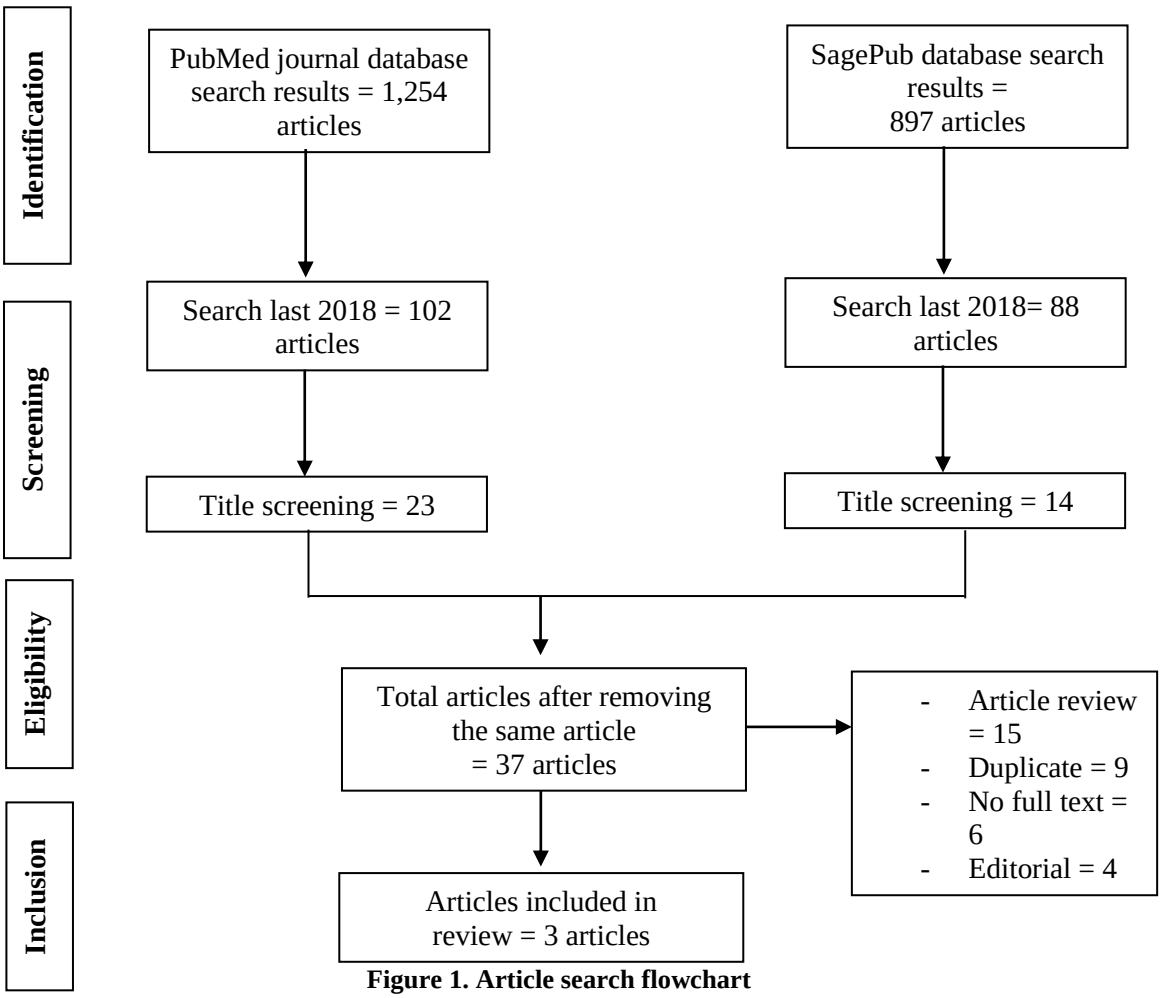

Figure 1. Article search flowchart

Quality Assessment and Data Synthesis

The writers independently examined a subset of the research in the titles and abstracts of the papers to pick which to evaluate. To choose papers for the systematic review, the entire texts of those that meet the inclusion criteria will be assessed. This will determine which publications to review. This answers "Which studies qualify for consideration for inclusion in the review?"

RESULT

We found three of the most relevant studies among all the studies that exist today. We present these studies in the table below.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Result
Song, 2020[11]	Singapore	Cross-sectional study	8222 women from this cohort who had natural menopause	Compared with those who had never used oral contraceptives, women with short-term use (≤5 years) of oral contraceptives had 26% lower odds of having cognitive impairment (odds ratio, 0.74; 95% confidence interval, 0.63-0.87), whereas the association was not statistically significant for those used for more than 5 years (odds ratio, 0.87; 95% confidence interval, 0.68-1.13). Women who used hormone-replacement therapy had a 39% lower odd of getting

				cognitive impairment compared with nonusers (odds ratio, 0.61; 95% confidence interval, 0.46-0.80).
Xi, 2022[12]	China	Cross-sectional study	4,275 women aged ≥65 years who had natural menopause	Longer reproductive periods and higher menopausal ages significantly reduced the risk of AD and MCI, while having more parities significantly increased the risk of dementia (odds ratio [OR] = 1.162, 95% confidence interval [CI]: 1.061–1.271, p = 0.001), specific AD (OR = 1.131, 95% CI: 1.010–1.266, p = 0.032), dementia with Lewy bodies (DLB) (OR = 1.238, 95% CI: 1.003–1.528, p = 0.047), vascular dementia (VaD) (OR = 1.288, 95% CI: 1.080–1.536, p = 0.005), and MCI.
Alexander, 2024[13]	Canada	Retrospective observational study	8,360 postmenopausal female participants (mean age at baseline = 65.0 ± 8.53 years, mean age at menopause = 50.1 ± 4.62 years) and 8,360 age-matched male participants for comparison	Early menopause and higher vascular risk were synergistically related with worse cognitive scores at follow-up (β = 0.013, 95% CI 0.001-0.025, p = 0.03). For women with early menopause, vascular risk was associated with worse cognitive scores in stratified analyses (menopausal ages 35-48 years; β = -0.044, 95% CI -0.066 to -0.022, p < 0.001), but not average (ages 49-52 years; β = -0.007, 95% CI -0.027 to 0.012, p = 0.46) or later menopause (ages 53-65 years; β = 0.003, 95% CI -0.020 to 0.025, p = 0.82). Female individuals with earlier menopause had a higher negative correlation of vascular risk with cognition than age-matched male participants. HT history did not alter the synergistic interaction of menopause age and vascular risk with follow-up cognition (β = -0.005, 95% CI -0.032 to 0.021, p = 0.69).

DISCUSSION

For women who went through menopause before 45, 45-49 years, and >54 years, the odds ratios (95% CI) for cognitive impairment were 1.67 (1.32-2.11), 1.24 (1.08-1.44), and 1.06 (0.87-1.29), respectively, compared to women who went through menopause between 50 and 54. According to Song et al. (2020). According to this, hormonal and reproductive issues that affect Singaporean Chinese women's reproductive health are linked to cognitive impairment later in life.[11] Xi, et al (2022)[12] found 28.6% of older women had MCI and 11.4% dementia. Early menarche, early menopause, shorter reproductive periods, and more pregnancies/parities were linked to cognitive decline and an increased risk of mild cognitive impairment (MCI) and dementia, particularly Alzheimer's disease (AD), DLB, and vascular dementia (VaD).[6] Other studies found a higher negative correlation between vascular risk and cognition in early menopausal women than males. HT history did not modify the influence of menopause age, vascular risk, or follow-up cognition (β = -0.005, 95% CI -0.032 to 0.021, p = 0.69). Cognitive impairment is more common in adult women, and their findings show endocrine

and vascular systems operate together. We discuss how these findings can inform gender-specific dementia prevention methods.[13] Cognitive complaints increased with menopause due to decreased attention, language, and working memory, and medial temporal lobe volume. In women who had estrogen-decreasing therapies, working memory and executive functioning problems increased. The evidence suggests that menopause, ovarian hormone loss, cognitive impairments, and SCD may be linked. More research is needed. Clinicians should monitor cognitive difficulties during menopause or ovarian hormone reduction since they may indicate future cognitive loss.[14]

Menopausal hormone therapy (MHT) with conjugated equine estrogens and medroxyprogesterone acetate tripled the risk of dementia and AD in postmenopausal women over 65 who were comorbid. Women's Health Initiative Memory Study found this. Overall, MHT reduces dementia risk and improves prevention. MHT for cognitive enhancement in non-dementia women can be safely administered by medical specialists. Demented ladies should not receive cognitive improvement MHT. Recent MHT and dementia research should inform international recommendations.[15] Increasing evidence suggests estrogen protects and improves the CNS. Working memory, concentration, processing speed, and verbal memory are impaired in menopausal women.[16] This article briefly discusses estrogens' biological roles in cognitive function and how they act. Estrogen affects the brain via nuclear and membrane pathways. Traditional estrogen modulates gene transcription via nuclear receptors. Different ligands and selective ER modulators have different binding affinities for ER α and ERβ.[17]

Steroids regulate neuropeptide, neuroactive transmitter, and receptor synthesis, secretion, and metabolism via genetic pathways in neurons. The high-affinity membrane-associated G-protein coupled ER GPR30/GPER1 may enable nongenomic estrogen activity and unique intracellular signaling cascades. Estrogens rapidly affect neuronal and pituitary cell excitability, activate cyclic adenosine monophosphate and mitogen-activated protein kinase (MAPK) pathways for kainite and IGF-1 receptors, modulate G-protein coupling, calcium currents, calcium channels, and calcium ion entry, and protect neurons from excitotoxins and free radical cells.[18,19]

By genetically regulating neuropeptide, neuroactive transmitter, and receptor production, release, and metabolism, steroids affect neurons. Nongenomic estrogen action and novel intracellular signaling cascades may be enabled by the high-affinity membrane-associated G-protein coupled ER GPR30/GPER1.[20] Estrogens rapidly affect neuronal and pituitary cell excitability, activate kainite and IGF-1 receptor cyclic adenosine monophosphate and MEK pathways, modulate G-protein coupling, calcium currents, calcium channels, and calcium ion entry, and protect neurons from excitotoxins and free radicals. Less estradiol affects three systems. We must determine if therapeutic estrogen regulation harms cognition. Hypoestrogenism affects basic forebrain cholinergic, dopaminergic, and mitochondrial bioenergetics and cognitive aging.[19]

Clinical studies suggest that glucose metabolism failure may drop estrogen levels and impair cognition. Low-grade inflammation may impair cognition. In postmenopausal women, IL-1, IL-6, and TNF-α levels increase. Sex HT may reduce inflammation by reducing inflammatory markers.[18,19] Estrogen may help us think sharply as we age. Estrogens protect the brain by regulating neuropeptides, neurotransmitters, and neurosteroid hormones, reducing cell death, promoting neuron development, regulating mitochondrial function, having antioxidant properties, modulating the immune system, and reducing β-amyloid production. Selective estrogen receptor modulators like tamoxifen and raloxifene interact with ERα,

ERβ, and GPR30, providing neuroprotection.[18,19]

In some cognitive domains, selective estrogen receptor modulators (SERM) suppress anticholinergic and proinflammatory cytokines. Testosterone reduces inflammation and protects neurons, research shows. To protect against oxidative stress, serum deprivation-induced apoptosis, and Aβ damage, testosterone acts via estrogen. Neprilysin, an Aβ-degrading enzyme, is activated by testosterone-induced damage via androgen receptors. Age, dosage, and duration affect female testosterone study results.[10,18] Exogenous testosterone affects verbal learning and memory in postmenopausal women, according to observational and interventional studies. The aromatization of estradiol does not appear to affect the effects of testosterone on postmenopausal women's language acquisition and memory.[10]

CONCLUSION

Changing hormone levels and cognition during menopause indicate a complex biological process. Estrogen protects and strengthens the central nervous system, according to growing evidence. Postmenopausal women have trouble with working memory, focus, processing speed, and verbal memory.

Declaration by Authors

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REFERENCES

1. Critchley HOD, Babayev E, Bulun SE, Clark S, Garcia-Grau I, Gregersen PK, et al. Menstruation: science and society. Am J Obstet Gynecol. November 2020;223(5): 624–64.
2. Levine L, Hall JE. Does the environment affect menopause? A review of the effects of endocrine disrupting chemicals on menopause. Climacteric. 2023;26(3):206–15.
3. Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. J Clin Endocrinol Metab. 2021;106(1):1–15.
4. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. Climacteric. 2019;22(4):403–11.
5. Hardy R, Mishra G, Kuh D. Life course risk factors for menopause and diseases in later life. In: Menopause, postmenopause and ageing. CRC Press; 2024. hal. 11–9.
6. Gannon OJ, Naik JS, Riccio D, Mansour FM, Abi-Ghanem C, Salinero AE, et al. Menopause causes metabolic and cognitive impairments in a chronic cerebral hypoperfusion model of vascular contributions to cognitive impairment and dementia. Biol Sex Differ. 2023;14(1):34.
7. Sochocka M, Karska J, Pszczołowska M, Ochnik M, Fułek M, Fułek K, et al. Cognitive Decline in Early and Premature Menopause. Vol. 24, International Journal of Molecular Sciences. 2023.
8. Sahab-Negah S, Hajali V, Moradi HR, Gorji A. The impact of estradiol on neurogenesis and cognitive functions in Alzheimer's disease. Cell Mol Neurobiol. 2020;40:283–99.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington VA: American Psychiatric Association; 2013.
10. Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L. Menopause and cognitive impairment: A narrative review of current knowledge. World J psychiatry. Agustus 2021;11(8): 412–28.
11. Song X, Wu J, Zhou Y, Feng L, Yuan J-M, Pan A, et al. Reproductive and hormonal factors and risk of cognitive impairment among Singapore Chinese women. Am J Obstet Gynecol [Internet]. 2020;223(3):410.e1-410.e23. Tersedia pada: https://www.sciencedirect.com/science/article/pii/S0002937820302209
12. Xi H, Gan J, Liu S, Wang F, Chen Z, Wang X-D, et al. Reproductive factors and cognitive impairment in natural menopausal women: A cross-sectional study. Front

Endocrinol (Lausanne) [Internet]. 2022;13. Tersedia pada: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2022.893901
13. Wood Alexander M, Wu C-Y, Coughlan GT, Puri T, Buckley RF, Palta P, et al. Associations Between Age at Menopause, Vascular Risk, and 3-Year Cognitive Change in the Canadian Longitudinal Study on Aging. Neurology [Internet]. 14 Mei 2024;102(9):e209298. Tersedia pada: https://doi.org/10.1212/WNL.0000000000209298
14. Reuben R, Karkaby L, McNamee C, Phillips NA, Einstein G. Menopause and cognitive complaints: are ovarian hormones linked with subjective cognitive decline? Climacteric [Internet]. 4 Juli 2021;24(4):321–32. Tersedia pada: https://doi.org/10.1080/13697137.2021.1892627
15. Stute P, Wienges J, Koller A-S, Giese C, Wesemüller W, Janka H, et al. Cognitive health after menopause: Does menopausal hormone therapy affect it? Best Pract Res Clin Endocrinol Metab [Internet]. 2021;35(6):101565. Tersedia pada: https://www.sciencedirect.com/science/article/pii/S1521690X21000828
16. Bortz J, Klatt KC, Wallace TC. Perspective: estrogen and the risk of cognitive decline: a missing choline (rgic) link? Adv Nutr. 2022;13(2):376–87.
17. Nguyen DH, Cunningham JT, Sumien N. Estrogen receptor involvement in vascular cognitive impairment and vascular dementia pathogenesis and treatment. Geroscience. 2021;43(1):159–66.
18. Baumgartner NE, Daniel JM. Estrogen receptor α: a critical role in successful female cognitive aging. Climacteric. 2021;24(4):333–9.
19. Peters BA, Santoro N, Kaplan RC, Qi Q. Spotlight on the gut microbiome in menopause: current insights. Int J Womens Health. 2022;1059–72.
20. de Souza Macêdo PR, Rocha TN, Fernandes SGG, Vieira MCA, Jerez-Roig J, da Câmara SMA. Possible association of early menopause with worse physical function: a systematic review. Menopause. 2021;28(4):467–75.

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