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Review

The neurobiology of menopause: Implications for brain aging and Alzheimer's risk

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SUMMARY

A growing body of evidence implicates the menopausal transition as a neurobiological inflection point in women's brain aging and Alzheimer's disease (AD) vulnerability. Menopause is a midlife neuroendocrine transition characterized by a decline in sex steroid hormones and widespread systemic effects. The brain is not a passive recipient of ovarian hormones but an active endocrine-sensing organ. Menopause, however, does not act in isolation: the ovarian-brain axis is established embryonically, activated at puberty, remodeled during pregnancy and postpartum, and reconfigured during the menopausal transition, with implications for later-life brain aging. This review places menopause within a lifespan neuroendocrine framework, examining mechanisms by which the transition may influence the brain, including altered hormone signaling, bioenergetics, synaptic plasticity, neurovascular function, inflammation, and AD-related pathology. It then reviews evidence linking menopausal timing to neurobiological and AD vulnerability, discusses estrogen therapy, and considers menopause as a biologically plausible window for risk stratification and prevention.

MENOPAUSE AS AN INFLECTION POINT FOR BRAIN AGING AND ALZHEIMER'S RISK

Accumulating data implicate the menopause transition as a critical inflection point in-brain aging and the risk of neurodegenerative disease.[1,2] Menopause is a universal neuroendocrine transition, marking the permanent cessation of ovarian cyclicity and a sustained decline in ovarian sex steroid hormones, 17β-estradiol (E2) and progesterone, accompanied by a compensatory rise in pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[3] Far from an isolated reproductive endpoint, this endocrine reorganization affects virtually every organ system, including cardiovascular and metabolic homeostasis, synaptic architecture, the system of organs required for immune function, and epigenetic aging trajectories.[1,2]

In the brain, menopause marks a phase of accelerated cellular aging[1] accompanied by a reorganization of metabolic activity, neuroendocrine signaling, neuroprotective capacity, and neurovascular function.[2,4,5] These changes may contribute to women's approximately 2-fold greater lifetime risk of Alzheimer's disease (AD), the leading cause of dementia, affecting ~55 million people worldwide.[6] Nearly two-thirds of all AD patients are women,[7] a disparity not fully explained by their greater longevity. A woman aged 45 already faces a lifetime risk of developing AD of 1 in 5, compared with 1 in 10 for a man of the same age.[7] As AD is now understood to begin in midlife, with pathological changes accumulating silently for decades before clinical symptoms emerge,[1,2,8] the overlap between this preclinical window and the typical timing of the menopausal transition has renewed interest in female neuroendocrine aging as a potential contributor to later vulnerability. Menopause occurs on average at age 51–52, with the preceding transition (perimenopause) spanning the mid-to-late 40s.[3] That the window of accruing AD risk overlaps with the typical onset of the menopause transition suggests that menopause may be more than a correlate of disease risk, and instead may represent a biological contributor.[9] This review examines the available evidence for this possibility while distinguishing mechanistic and preclinical findings from observational studies and clinical trials in humans.

Ovarian sex steroid hormones have long been examined as pivotal to this vulnerability. E2 in particular acts throughout the brain as a pleiotropic neuromodulator, supporting mitochondrial function, synaptic plasticity, cerebrovascular integrity, and anti-inflammatory tone.[10,11] The permanent decline in E2 following menopause may remove a broad neuroprotective influence at around the age when Aβ and tau pathology begin to accumulate. The timing of this withdrawal—and whether exogenous hormone replacement can recapitulate the neuroprotective signal—has emerged as one of the most debated and clinically consequential questions in neurology and is a central focus of this review.

That question cannot be addressed, however, by considering menopause in isolation. The neurological impact of hormone withdrawal depends not only on changes in specific hormones themselves but also on the neuroendocrine system that has been shaped to receive and respond to those signals across the female lifespan. From this perspective, menopausal vulnerability is not a self-contained phenomenon but the consequence of an ovarian-brain axis that has been organized before birth, amplified at puberty, dynamically reorganized during pregnancy and the postpartum period, and partially dismantled across the

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menopausal transition. Understanding menopause as the culmination of this lifelong dialog, and in the context of the many biological and environmental exposures that contribute to shaping it, may help clarify who is at risk, when that risk peaks, and how it might be modified. This review situates menopause within a lifespan neuroendocrine framework, discussing the preclinical mechanisms by which menopause reshapes the aging brain, the clinical and neuroimaging evidence linking menopausal timing and hormone exposures to AD risk, and the emerging evidence that the transition may represent a biologically relevant window for AD risk stratification and prevention research in women.

THE OVARIAN-BRAIN AXIS: HARDWIRED FROM THE START

The relationship between the ovary and the brain is established in the earliest stages of embryonic development, underscoring this axis as a central structural feature of the nervous system. The gonadotropin-releasing hormone (GnRH) neurons that will ultimately orchestrate reproductive function appear to arise in the olfactory placode and migrate along olfactory and vomeronasal axons to reach their permanent locations in the preoptic area and medial hypothalamus during fetal life.[12] This process involves a coordinated network of molecular guidance cues, including semaphorins, hepatocyte growth factor, and related signaling pathways.[12,13] The kisspeptin system, encoded by KISS1 and acting through its receptor KISS1R, is considered the master regulator of GnRH pulsatility and a key interface through which the brain integrates metabolic and hormonal signals.[14,15] Kisspeptin neurons in the arcuate nucleus and anteroventral periventricular nucleus integrate inputs from E2, progesterone, leptin, and insulin, transducing them into patterned GnRH release.[14,15] In the arcuate nucleus, kisspeptin neurons co-express neurokinin B and dynorphin (the KNDy triad) forming a self-sustaining pulse generator that governs the frequency and amplitude of hypothalamic-pituitary-gonadal (HPG) axis activity.[16] In this axis, pulsatile GnRH release from the hypothalamus stimulates the pituitary secretion of FSH and LH, which, in turn, regulate ovarian folliculogenesis, ovulation, and steroid hormone production. This tightly coordinated neuroendocrine network establishes the hormonal rhythm that will regulate reproductive function, associated brain signaling, and endocrine homeostasis from puberty through menopause.

The genetic architecture of the ovarian-brain axis further suggests that the two systems share aspects of their molecular infrastructure from the outset. Variations in estrogen receptor (ER) genes have been associated with both reproductive aging and AD-related outcomes,[17–19] raising the possibility that ovarian and neuronal aging share aspects of their genetic architecture. A 10-year longitudinal study further reported that variations across all ER genes—ESR1, ESR2, and G-protein-coupled estrogen receptor 1 (GPER1)—were associated with cognitive decline and increased tau pathology.[19] Fragile X messenger ribonucleoprotein 1 (FMR1) provides another example, as women carrying FMR1 premutations (55–200 CGG repeats) have elevated rates of premature ovarian insufficiency and are also at increased risk of fragile X-associated tremor/ataxia syndrome, a neurodegenerative disorder with features of parkinsonism and cognitive decline.[20] Turner syndrome (45,X), in which ovarian dysgenesis is accompanied by a distinctive cognitive profile affecting visuospatial and executive function, further illustrates how X-chromosome dosage shapes both ovarian reserve and brain circuit organization from the earliest stages of development.[21]

Notably, the ovary-brain axis is fundamentally bidirectional (Figure 1). The classical model positions the brain as the governing organ, in which hypothalamic GnRH drives pituitary gonadotropin release, which in turn regulates ovarian steroidogenesis.[2,4,5] However, E2 and progesterone released from the ovary act extensively on the brain, shaping neuronal morphology, synaptic density, myelination, neurotransmitter synthesis, and cerebrovascular tone across the lifespan.[2,4,5] ERs are expressed across virtually every major brain region from early in development, and neural circuits are sensitive not only to the presence or absence of estrogenic signaling but also to its pattern, timing, and amplitude.[10,11] This bidirectionality means that disruption at any stage—through genetic variation, premature ovarian insufficiency, oophorectomy, or medical and pharmaceutical interventions—can carry consequences that are simultaneously reproductive and neurological.

Neuroendocrine aging across the female lifespan is best understood as a progression marked by major turning points. As reviewed below, puberty, pregnancy, the postpartum period, and perimenopause each represent discrete, biologically programmed phases during which the ovarian-brain axis is recalibrated under markedly different hormonal conditions, producing structural, functional, and metabolic adaptations in the brain. These transitions vary in scope and duration, but all involve periods of heightened plasticity during which endocrine signals reorganize neural circuits and physiological set points. Perimenopause is distinctive in that it represents the final transition in this sequence, yet it emerges from mechanisms and pathways that have been engaged repeatedly across the reproductive lifespan.

PUBERTY: SYSTEM ACTIVATION

After a period of relative quiescence during childhood, the HPG axis is reactivated at puberty through disinhibition of hypothalamic kisspeptin neuron activity and the emergence of pulsatile GnRH secretion.[16] In girls, the resulting estrogen surge drives a cascade of somatic and neural changes that helps establish the hormonal environment in which the body and brain will operate for the next three to four decades.[22] Pubertal E2 exposure is associated with accelerated myelination of prefrontal-limbic pathways, synaptic pruning within cortical circuits, and elaboration of dendritic arbors in regions such as the hippocampal and amygdala neurons—changes that collectively refine the neural substrates of memory, executive function, and affective regulation.[23] At the macroscale, puberty initiates a prolonged phase of brain remodeling characterized by synaptic pruning, cortical gray matter (GM) reduction and thinning, and continued white matter (WM) maturation.[22–24] These trajectories follow an inverted-U pattern for GM and continued growth and refinement for WM, beginning around puberty but not fully stabilizing until late adolescence or early adulthood.[22–24]

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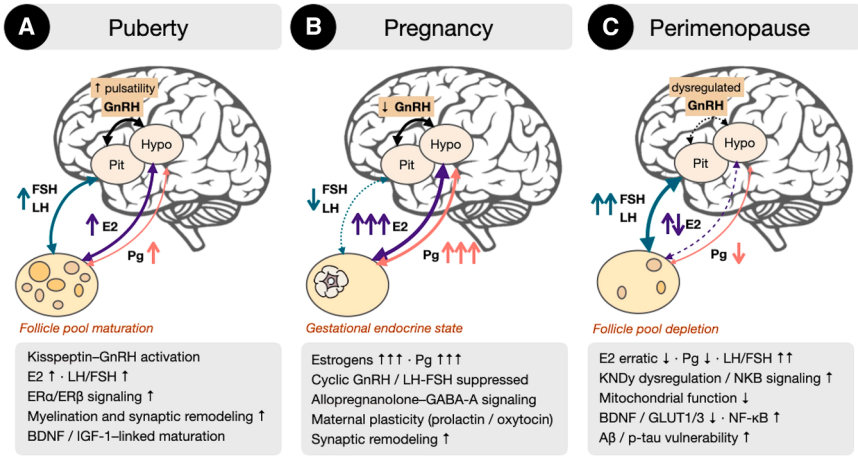


Figure 1. Bidirectional brain-ovary signaling across key reproductive transitions

Schematic of hypothalamic-pituitary-ovarian signaling during (A) puberty, (B) pregnancy, and (C) perimenopause. Arrows indicate conceptual changes in GnRH, FSH/LH, estradiol, and progesterone signaling; line thickness reflects relative signal strength. Boxes summarize selected brain processes associated with each stage. Trajectories are conceptual rather than quantitative.

Abbreviations are as follows:Aβ, amyloid-β; E2, 17β-estradiol; ER, estrogen receptor; GLUT, glucose transporter; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; HYPT, hypothalamus; LH, luteinizing hormone; Pg, progesterone; p-tau, phosphorylated tau.

These processes are partly sexually dimorphic: girls enter puberty, on average, approximately 2 years earlier than boys, and trajectories of WM maturation and cortical thickness differ by sex in ways that persist into adulthood.[24] Additionally, pubertal development is associated with marked changes in endothelial function, blood pressure regulation, and body-composition-related vascular demand, as well as cerebral perfusion, with sex-divergent trajectories emerging during adolescence and appearing in part attributable to pubertal maturation rather than chronological age alone.[25]

Overall, puberty is both a key reproductive event and a period of neural remodeling during which the ovarian-brain axis is activated, calibrated, and set to a new functional baseline from which subsequent hormonal transitions will unfold. Some features of puberty itself, such as the timing of its onset, may carry neurological relevance beyond the immediate developmental window. Age at menarche has been associated with cognitive trajectories in later life,[26,27] suggesting that the hormonal environment established during puberty may leave a lasting imprint on brain aging. Puberty is also a period during which psychiatric conditions relevant to later cognitive health may first emerge. For example, depression and anxiety increase markedly during adolescence, particularly among girls, and both have been associated with elevated risk of cognitive decline and dementia later in life.[22] Although these associations are unlikely to be explained by pubertal hormones alone, the convergence of neuroendocrine remodeling, stress-system maturation, and the onset of affective vulnerability suggests that puberty may establish trajectories with consequences extending well beyond adolescence.[22]

Puberty also marks the beginning of the cyclical hormonal pattern that defines the neuroendocrine milieu of adulthood. Each menstrual cycle exposes the brain to a coordinated sequence of E2 rise, gonadotropin surge, and progesterone peak—and circuits across the limbic system, prefrontal cortex, and brainstem respond dynamically through changes in receptor signaling, synaptic density, and neurotransmitter tone.[28] Over years of cyclicity, the brain develops a decades-long hormonally conditioned functional state that may be transiently reorganized during pregnancy and is ultimately destabilized by menopause.

PREGNANCY AND THE POSTPARTUM PERIOD

If puberty establishes the hormonal baseline of adulthood, pregnancy represents its most extreme perturbation. Circulating estradiol rises approximately 100-fold to 1,000-fold during pregnancy, reaching concentrations that exceed those of any other physiological state, while progesterone, human chorionic gonadotropin, oxytocin, and prolactin rise in parallel, collectively transforming the neuroendocrine environment throughout gestation.[29] Pregnancy is also distinguished by a marked rise in estriol (E3), the predominant circulating estrogen of gestation, produced largely through coordinated fetal-placental steroidogenesis.[29] Pregnancy and the postpartum period together comprise matrescence, a major biopsychosocial and neuroendocrine transition associated with extensive maternal brain remodeling.[30]

Longitudinal neuroimaging studies have documented GM volume (GMV) reductions across extensive cortical networks during pregnancy that persist for at least 2 years postpartum and show specificity for regions supporting social cognition and theory of mind.[31] These changes have been interpreted as reflecting adaptive synaptic pruning—a sharpening of circuits relevant to maternal caregiving—and their extent correlates with maternal-infant attachment.[31] A recent longitudinal study spanning pre-, during, and post-pregnancy, with follow-up extending beyond 2 years, documented an inverted-U trajectory in GMV with partial recovery over time, in association with plasma estrogen levels.[32] A study mapping the course of a human pregnancy from preconception through 2 years postpartum showed pronounced and diffuse decreases in GMV and cortical thickness, paralleled by increases in WM microstructural integrity, ventricle volume, and cerebrospinal fluid (CSF).[33] Pregnancy thus suggests that the adult brain retains substantial capacity for large-scale hormone-related remodeling well into adulthood.

Pregnancy also involves substantial systemic vascular and metabolic changes alongside more constrained central nervous system (CNS) adaptation.[34] In the periphery, large-scale vascular remodeling, including reduced systemic vascular resistance, increased uteroplacental blood flow, endothelial adaptation, and remodeling of resistance vessels, accommodates the

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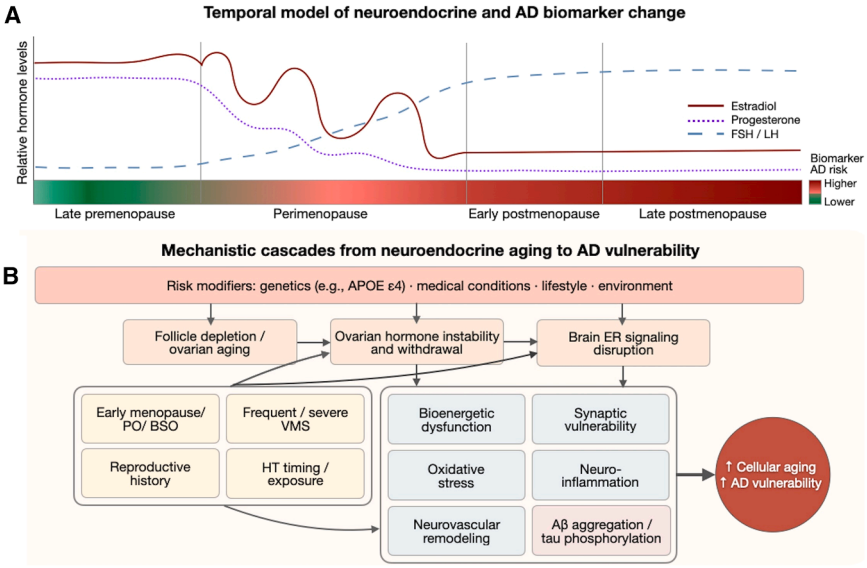


Figure 2. Menopause-related neuroendocrine and biomarker vulnerability relevant to later Alzheimer's disease risk

(A) Conceptual trajectories of estradiol, progesterone, and FSH/LH from late premenopause through postmenopause, shown alongside a qualitative gradient of AD-biomarker vulnerability (green = low to red = high).

(B) Proposed pathways linking ovarian aging and hormone instability to altered brain ER signaling, bioenergetic, synaptic, inflammatory, vascular, and AD-related changes. Genetic, medical, lifestyle, and reproductive factors are shown as modifiers rather than established causal determinants. Curves and arrows indicate conceptual directionality, not effect size.

Abbreviations are as follows:AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; Aβ, amyloid-beta; BSO, bilateral salpingo-oophorectomy; ER, estrogen receptor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HT, hormone therapy; PO, premature oophorectomy; VMS, vasomotor symptoms.

major hemodynamic demands of gestation.[34] In the brain, changes in vascular reactivity, myogenic tone, and blood-brain barrier regulation help preserve relatively stable cerebral blood flow (CBF).[34] Pregnancy can also unmask cardiometabolic vulnerability: gestational hypertension, preeclampsia, and gestational diabetes are associated with elevated long-term risks of hypertension, type 2 diabetes, cerebrovascular disease, and cognitive impairment.[9] These conditions need to be more thoroughly investigated as early-life "stress tests" of vascular and metabolic resilience and vulnerability associated with later cerebrovascular, cognitive, and dementia risk.

At the molecular level, pregnancy engages many of the same neuroendocrine pathways first activated at puberty but at far greater amplitude. Rising hormones reshape gene transcription, synaptic plasticity, neuroimmune tone, and cellular metabolism across hypothalamic, limbic, and cortical circuits.[35] These signals act through overlapping receptor systems—including ERα, ERβ, progesterone receptors, glucocorticoid receptors, and GABA-A receptor modulation by the progesterone metabolite allopregnanolone—to alter dendritic remodeling, inhibitory-excitatory balance, and stress responsivity.[35] Pregnancy therefore offers a physiologic model of large-scale hormone-driven brain plasticity and neural adaptation, whereas the postpartum period may reveal the consequences of withdrawal from that state.

The neurological consequences of pregnancy and parity remain under active investigation as potential modulators of brain aging and later-life AD risk, as the direction and magnitude of this association vary across studies and may depend on the timing, number, and hormonal characteristics of pregnancies.[9,36,37] What the data more consistently demonstrate is that the hormonal surges of pregnancy, and perhaps more so the fairly abrupt withdrawals that follow, may leave lasting traces on neural organization. For instance, the loss of placental E2 and progesterone may render the postpartum brain vulnerable to mood dysregulation.[38] Women who experience postpartum depression (PPD) may also be more vulnerable to mood disruption at other hormonal inflection points, such as perimenopause.[39] Although direct empirical evidence linking pregnancy-related cognitive changes to later menopausal cognitive vulnerability is limited, there are similarities worth noting. A substantial proportion of pregnant women and new mothers report subjective cognitive difficulties, colloquially termed "mommy brain," including slowed processing speed and reduced working memory and prospective memory.[30] Objective neuropsychological testing has confirmed modest but measurable deficits in memory and executive function during pregnancy that generally resolve postpartum or in later years[30] and likely reflect a combination of hormone-driven circuit remodeling, sleep disruption, and related physiological demands.

MENOPAUSE AND THE AGING BRAIN

Menopause is the last major neuroendocrine transition the female brain undergoes and the only one characterized by permanent loss of ovarian cyclicity and sustained withdrawal of ovarian sex steroids. Perimenopause is defined by the STRAW+10 staging system as the period of menstrual irregularity and hormonal flux preceding the final menstrual period (FMP), typically spanning 4 to 8 years and culminating in 12 consecutive months of amenorrhea (menopause).[40] What distinguishes perimenopause from the hypoestrogenic plateau of postmenopause is cycle-to-cycle variability, with peak E2 concentrations in some perimenopausal cycles exceeding those of typical reproductive cycling, superimposed on an erratic rise in FSH and LH as the pituitary attempts to compensate for waning ovarian reserve.[3] Beyond E2, declining progesterone and altered neurosteroid signaling also contribute to the neurobiology of the menopausal transition. Progesterone and its metabolite allopregnanolone modulate GABA-A receptor activity, inhibitory-excitatory balance, stress responsivity, sleep, and affective function.[3] Because progesterone decline often precedes sustained E2 withdrawal[3] (Figure 2), disruption of progesterone-allopregnanolone signaling may

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contribute to neurological and affective symptoms during perimenopause, although its implications for AD-related pathways remain less well characterized than those of estrogen. Additionally, increased hypothalamic GnRH signaling and pituitary secretion of FSH and LH act to stimulate follicular recruitment and ovarian steroidogenesis in an effort to preserve reproductive function.[3] As ovarian responsiveness declines, however, gonadotropin levels remain chronically elevated.[3] All these changes may constitute a neurobiological stressor: the brain, calibrated over decades to a cyclical and broadly predictable hormone signal, appears to register the unpredictability of the perimenopausal milieu as an energetic and synaptic challenge, initiating responses that in preclinical literature appear to be both adaptive and maladaptive, as discussed below.[2,4,5,41]

ER signaling in the brain

ERα and ERβ are distributed throughout the CNS, with particularly dense expression in pituitary, hypothalamus, hippocampus, amygdala, prefrontal cortex, and locus coeruleus—regions central to memory, affect, and cholinergic modulation.[10,11] ERα predominates in hypothalamic nuclei governing the HPG axis and in limbic circuitry, while ERβ is more widely represented across cortical and hippocampal regions as well as glia, including oligodendrocytes and astrocytes.[42] GPER mediates rapid non-genomic estrogen signaling at the plasma membrane, activating kinase cascades, including PI3K/Akt and MAPK/ERK, within minutes of E2 exposure.[43]

This dual mode of estrogen action—slow, transcriptional (genomic) and fast, kinase-mediated (non-genomic)—confers flexibility in the neuronal response to fluctuating hormone levels.[10,11] Importantly, ER expression in the adult brain is neither static nor uniform: it is shaped by age, brain region, and circulating E2 levels, with declines in nuclear ER expression reported in older female animals.[10,11] Experimental studies further show that ER expression varies across the estrous cycle and can be modulated by exogenous as well as endogenous estrogen exposure, indicating that the brain's estrogen sensitivity is itself hormonally regulated.[44] During perimenopause, as E2 levels become erratic before their final decline, this signaling architecture is progressively destabilized. One of the clearest signatures of this transition involves once again the hypothalamic KNDy network.[16] As estrogen feedback wanes, this circuitry becomes dysregulated, with disrupted GnRH pulsatility and disinhibited neurokinin B signaling, which contribute not only to gonadotropin instability but also to vasomotor symptoms (VMS, e.g., hot flashes).[45] Through projections to thermoregulatory regions in the preoptic hypothalamus, hyperactivity of KNDy neurons is thought to narrow the thermoneutral zone and trigger exaggerated heat-dissipation responses, providing a mechanistic framework for the hot flashes that characterize the menopausal transition.[45] The efficacy of neurokinin 3 receptor (NK3) antagonist fezolinetant (Veozah) and the dual NK1/NK3 receptor antagonist elinzanetant (Lynkuet), both non-hormonal treatments for menopausal VMS, provides clinical support for this model and identifies KNDy circuitry as a mechanistically relevant target in menopause.[46] Whether modulation of this circuitry influences brain aging or AD risk remains unknown.

Mitochondrial bioenergetics and brain metabolism

Another effect of E2 withdrawal is its impact on mitochondrial function and cerebral energy metabolism.[2,4,5,41] E2 enhances mitochondrial oxidative phosphorylation, promotes expression of electron transport chain subunits, and maintains mitochondrial membrane potential in neurons—effects mediated largely through ERβ-dependent transcription of mitochondria-related genes and non-genomic activation of Bcl-2 family proteins.[2,4,5,41] In the "healthy cell bias" framework, E2 promotes neuronal survival and mitochondrial efficiency specifically in cells with intact metabolic machinery; once neurons are energetically compromised, the estrogenic signal may shift toward alternative, potentially maladaptive, pathways.[4,41] Mechanistic analyses have shown that E2 depletion induces a coordinated neurometabolic shift, leading to reduced neuronal mitochondrial respiration, altered expression of glucose transporters and oxidative phosphorylation genes.[4,41] This prompts declines in cerebral glucose utilization and increased mitochondrial reliance on less efficient fuel for ATP production, such as ketones, lipids, and amino acids.[47,48] Neurons must therefore sustain ATP production through increasingly inefficient pathways, with the resulting bioenergetic deficit leading to mitochondrial dysfunction, which, in turn, lowers the threshold for Aβ dysmetabolism, toxicity, and cellular apoptosis.[47]

E2 replacement, particularly when initiated within a defined window following ovariectomy, restores mitochondrial respiration, normalizes glucose transporter expression (GLUT3 and GLUT4), and reverses the metabolic deficit.[49,50] The molecular mediators include estrogen-responsive elements in the promoters of genes encoding cytochrome c oxidase subunits and pyruvate dehydrogenase complex components, as well as E2-driven expression of uncoupling protein 2 (UCP2), which buffers mitochondrial reactive oxygen species (ROS) production.[4,41]

Vascular remodeling

In the CNS, estrogen withdrawal has been linked to reductions in CBF velocity and cerebrovascular reactivity in human studies, while experimental menopause models show cerebral arteriolar dysfunction and impaired neurovascular coupling.[51] In the periphery, loss of ovarian hormones is associated with endothelial dysfunction, increased arterial stiffness, autonomic dysregulation, and altered blood pressure control, changes that appear more pronounced in women with frequent VMS and may be a risk factor for cardiovascular disease (CVD).[3] These parallel central and peripheral vascular shifts support the view that neuroendocrine aging is also a vascular transition, with consequences for both symptom burden and long-term AD-relevant risk.

Neuroinflammation and glial biology

Estrogen exerts potent anti-inflammatory actions in the CNS, primarily through suppression of nuclear factor (NF)-κB-mediated transcription of pro-inflammatory cytokines—including IL-1β, TNF-α, and IL-6—in microglia and astrocytes.[52,53] Microglia express both ERα and ERβ, and E2 shifts microglial activation away from pro-inflammatory states and toward more reparative phenotypes.[53] This immunomodulatory function is particularly relevant in the context of AD, where microglial activation and neuroinflammation play central roles in disease progression. Following

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ovariectomy, female rodents exhibit accelerated microglial activation, elevated hippocampal levels of IL-1β and TNF-α, and increased astrogliosis—changes attenuated by E2 replacement.[52,54] Sex differences in microglial density, morphology, and transcriptomic profiles are well established in both rodents and humans, with female microglia maintaining a more surveillant (ramified) morphology that becomes progressively reactive with E2 withdrawal.[54] These observations suggest that the menopausal decline in E2 removes the anti-inflammatory brake on glial activity, facilitating a neuroinflammatory milieu that amplifies Aβ and tau pathology.[53]

Synaptic plasticity and cholinergic vulnerability

Estrogen is a potent modulator of synaptic structure and function.[41,55] In hippocampal CA1 neurons, E2 drives formation of dendritic spines and potentiates NMDA receptor-mediated long-term potentiation (LTP) through both transcriptional and rapid non-genomic mechanisms.[10,11] These effects may depend on spine localization of ERα and engagement of the mGluR/PI3K/Akt pathway, and require intact brain-derived neurotrophic factor (BDNF)-TrkB signaling, with E2 increasing BDNF expression in the hippocampus and cortex.[10,11,56] Estrogen also exerts trophic effects on the basal forebrain cholinergic system, which provides the principal cholinergic innervation of the hippocampus and neocortex and is among the earliest systems affected in AD. E2 upregulates expression of choline acetyltransferase (ChAT), the vesicular acetylcholine transporter (VAChT), and nerve growth factor (NGF) receptors in basal forebrain neurons, whereas ovariectomy reduces cholinergic tone in hippocampal terminals—an effect reversed by E2 replacement.[57] Given that cholinergic deficits correlate closely with cognitive impairment in AD and represent the primary target of first-line pharmacotherapy (acetylcholinesterase inhibitors), E2's capacity to sustain this system has direct clinical relevance.

Amyloid and tau: Hormonal modulation of AD pathology

Preclinical evidence indicates that estrogen regulates key steps in both Aβ production and clearance.[58] E2 shifts amyloid precursor protein (APP) processing toward the non-amyloidogenic α-secretase pathway, reducing Aβ generation while simultaneously upregulating insulin-degrading enzyme (IDE) and neprilysin—the primary Aβ-degrading proteases—in hippocampal neurons.[58,59] Ovariectomy in transgenic AD model mice (APP/PS1, 3×Tg-AD) accelerates Aβ plaque deposition and increases soluble Aβ42 levels, whereas E2 replacement ameliorates these effects in a time-dependent manner, with efficacy diminishing when treatment is delayed.[60,61]

Estrogen's effects on tau are similarly documented. E2 inhibits glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5)—the principal tau kinases implicated in neurofibrillary tangle formation—and promotes tau dephosphorylation through upregulation of protein phosphatase 2A (PP2A).[62] In rodent models, E2 deprivation increases hippocampal tau phosphorylation at AD-relevant epitopes (Thr181, Ser202, and Thr231), and this hyperphosphorylation is reversed by E2 treatment.[63] These findings support the view that estrogen signaling modulates biochemical pathways implicated in AD pathology and that its loss at menopause may accelerate the accumulation of both hallmark lesions.

As mentioned above, the rise in gonadotropins that accompanies ovarian aging is initially a compensatory physiological response to reduced ovarian reserve and diminished estrogen and progesterone feedback.[3] Over time, however, chronically elevated gonadotropin levels may influence AD-related molecular pathways as FSH and LH promote amyloidogenic APP processing in experimental systems, whereas pharmacological suppression of gonadotropin signaling reduces Aβ pathology in animal models.[64,65] Thus, a response that is initially adaptive within the reproductive axis may become a parallel neurobiological stressor when prolonged.[64,65]

Translational research

An important translational limitation of preclinical research is that most animal models of menopause rely on ovariectomy and therefore investigate abrupt ovarian hormone loss rather than the gradual, fluctuating endocrine changes of spontaneous perimenopause. Findings from these models are highly informative mechanistically but cannot be assumed to recapitulate the timing or complexity of the human menopausal transition. Neuroimaging and biomarker studies have sought to translate this preclinical framework into measurable brain phenotypes in women. Aβ and tau positron emission tomography (PET) and CSF measures, MRI-derived volumetrics, and 18F-fluordeoxyglucose (FDG) PET of cerebral glucose metabolism (CMRglc) provide direct in-brain readouts of the neurobiological shifts documented above. Plasma Aβ42, Aβ40, p-tau217, p-tau181, total tau, and other markers are now analytically feasible at scale.

Cross-sectional biomarker studies of spontaneous menopause

As longitudinal studies prospectively mapping biomarker alterations across the menopausal transition remain sparse, available evidence linking menopause to AD risk derives mainly from cross-sectional comparisons across menopausal stages. Several structural MRI analyses document lower GMV in AD-vulnerable medial temporal structures tracking with menopausal stage, independent of chronological age.[66–81] In 18F-FDG PET studies of midlife women at risk for AD, including those with an AD family history and/or those carrying an apolipoprotein E epsilon 4 (APOE-4) allele, early postmenopausal and perimenopausal women exhibit lower CMRglc in the posterior cingulate cortex, precuneus, and lateral temporal regions—an anatomical signature closely mirroring the hypometabolic pattern of early AD—as well as frontal regions when compared with premenopausal women and age-controlled men.[66,68,69,72] PET studies also reveal subtle but measurable age-adjusted elevations in Aβ load in early postmenopausal women, and to a lesser extent perimenopausal women, relative to premenopausal controls and age-controlled men,[66,68,69,72] as well as higher tau levels with earlier age at menopause.[76] This is consistent with preclinical mechanisms linking neuroendocrine change to AD-related pathology at a stage that is nominally preclinical. However, these cross-sectional studies establish associations with menopausal stage but cannot determine whether the observed differences are caused by the menopausal transition, chronological aging, or correlated health and reproductive factors, among other factors.

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Longitudinal biomarker studies of spontaneous menopause

Longitudinal data remain very limited, representing a major gap in our understanding of the temporal dynamics of menopausal brain aging and in efforts to define the clinical significance of these alterations. To date, two biomarker studies have included longitudinal follow-ups. A multimodality neuroimaging study followed 41 midlife women and 18 age-controlled men for 3 years.[68] Over time, compared with men, both post- and perimenopausal groups exhibited higher rates of 18F-FDG PET CMRglc decline in AD regions, and the postmenopausal group also exhibited higher rates of hippocampal volume loss and Aβ deposition compared with men and premenopausal controls.[68] In keeping with preclinical work, CMRglc decline exceeded Aβ and hippocampal volume changes,[68] suggesting the emergence of a female-specific hypometabolic AD-endophenotype during the menopausal transition. A larger cross-sequential study (n = 161 women) with a 2-year follow-up component showed that postmenopausal women experienced a CMRglc decline in parietal regions compared with age-controlled men, along with relative stabilization in temporal regions.[72]

Prospective and retrospective oophorectomy studies

Stronger temporal inference is available from prospective oophorectomy studies, although these models represent abrupt hormone loss rather than the more gradual declines that accompany spontaneous menopause. Biomarker alterations tend to be more severe with early or premature menopause, primarily, but not exclusively, due to oophorectomy.[71,73–76] It is well documented that premenopausal bilateral oophorectomy (PO) and salpingo-oophorectomy (BSO) are linked with a higher risk of AD and dementia.[26,27] In neuroimaging studies, women with a history of PO exhibit lower medial temporal lobe volume,[71,82,83] reduced WM integrity,[71,84] and greater Aβ burden[69] compared with spontaneous, later-onset menopause. However, most studies analyzed data acquired years to decades after surgery, and most included MHT users, which precluded determining whether the observed brain abnormalities are attributable to the procedure itself or influenced by exogenous hormone use. Only one study to date has adapted a pre- vs. post-surgery study design, capturing brain changes more directly due to surgery. In a matched cohort study, women undergoing PO (n = 12) exhibited steeper declines in hippocampal and parahippocampal volume, steeper and accelerating declines in WM volume, and accelerated increases in superior frontal CBF relative to controls, together with steeper rises in LH and FSH that tracked with greater hypothalamic and medial temporal abnormalities.[85] These findings provide the first longitudinal evidence that abrupt ovarian hormone loss alters structural and functional brain trajectories in HPG-axis-relevant regions.[85] Larger studies with longer follow-up are needed to determine whether such changes persist, stabilize, or translate into long-term AD risk.

Additional findings

A higher postmenopausal WM hyperintensity (WMH) burden,[86] altered WM integrity profiles,[87] structural connectivity,[87] and brain mitochondrial ATP production[72,77] have also been reported. More limited observational findings also link FSH and LH elevations to higher AD-biomarker load in midlife women in association with menopausal stage.[88,89] Of note, studies including women specifically at the perimenopausal stage already show biomarker alterations across different modalities.[66–69,72,74,77,87] Although these abnormalities are less pronounced and more variable than those observed postmenopause, they include lower CMRglc and GMV in AD-vulnerable regions and, in some cohorts, elevations in Aβ levels.[66–69,72,74,77] Although more research is needed, these findings suggest that perimenopause may represent the earliest identifiable window of vulnerability—a stage at which compensatory adaptations are ongoing, yet measurable evidence of neurobiological stress is present.

Menopause-related symptoms

Observational studies also link the telltale symptom of menopause, VMS, with AD risk. Women with frequent or severe symptoms exhibit worse verbal memory performance, greater WMH burden, and higher plasma Aβ42 levels.[90,91] These associations position VMS as a candidate clinical biomarker for underlying neuroendocrine instability that may index biological risk for future cognitive decline in addition to or independently of hormonal levels per se.

Of note, up to 62% of postmenopausal and perimenopausal women report subjective cognitive decline (SCD) most frequently described as word-finding failures, impaired working memory, and reduced concentration.[92] These complaints are an important, though often overlooked, symptom of menopause. Objective neuropsychological testing corroborates a modest but reproducible dip in verbal learning and processing speed during the menopause transition,[92,93] which persists after controlling for VMS, disturbed sleep, and mood symptoms. Complementing these findings, in a neuroimaging study of 156 perimenopausal and postmenopausal midlife women at risk for AD, those with SCD exhibited worse verbal memory and executive function together with altered 31P-MRS mitochondrial bioenergetics in some AD-vulnerable regions, reflected by higher phosphocreatine-to-ATP ratios (e.g., reduced ATP production or inability to meet energy demands) in the precuneus, posterior cingulate, and parietal cortex.[94] Altered parietal ATP levels, menopause symptom severity, and VMS presence were the strongest correlates of SCD status.[94] Some longitudinal studies suggest that cognitive difficulties may be most pronounced during late perimenopause and may improve in later postmenopause.[92,93,95] However, the extent, timing, and completeness of recovery remain uncertain, and available findings do not establish that menopause-related cognitive changes are uniformly reversible.

Proteomic studies

Emerging data suggest that both menopause stage and menopause timing are associated with detectable blood-based molecular signatures relevant to brain aging and AD. In analyses of multiple cohorts, spontaneous menopause was associated with inflammatory, synaptic, metabolic, and AD-related proteomic shifts that tracked with E2 and FSH rather than chronological age and were linked to VMS, later-life cognitive outcomes, and plasma p-tau and Aβ measures.[96] Additionally, a separate preprint analysis of postmenopausal women from the UK Biobank (N = 15,012) showed that earlier menopause was associated with pro-inflammatory and extracellular matrix remodeling pathways, accelerated brain and oligodendrocyte aging clocks, and protein signatures that tracked with incident dementia risk, brain

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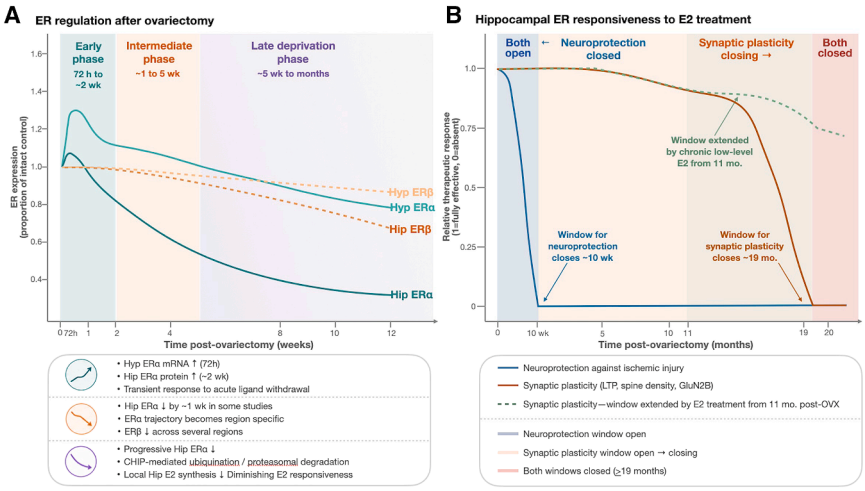


Figure 3. Temporal dynamics of estrogen receptor regulation after ovariectomy and endpoint-specific windows of E2 responsiveness in the rodent hippocampus

(A) ERα and ERβ expression trajectories in the hippocampus (Hip) and hypothalamus (Hyp) following ovariectomy (OVX) in female rodents, expressed as a proportion of the intact sham baseline (1.0). Curves represent consensus trends synthesized across relevant studies; intermediate time points are interpolated. Shaded regions denote three post-OVX phases: early (72 h to ~2 weeks), intermediate (~1–5 weeks), and late deprivation (~5 weeks to months). Hippocampal ERα (solid teal) shows a transient early upregulation in some studies, followed by progressive decline, reaching ~40% of sham in one study by 8 weeks.[101–104] Hippocampal ERβ (dashed orange) remains stable early and then declines gradually from ~4 weeks.[104,105] Hypothalamic ERα (solid light teal) shows pronounced mRNA upregulation at 72 h in the medial preoptic, arcuate, and ventromedial nuclei, reflecting acute de-repression following ligand withdrawal[100]†, followed by progressive protein-level decline with aging.[108] Hypothalamic ERβ (dashed light orange) declines gradually.[106,108] †72 h hypothalamic point = ERα mRNA by *in situ* hybridization; all other trajectories = protein by western blot or immunohistochemistry.

(B) E2 therapeutic responsiveness in the hippocampus following OVX, assessed by two distinct functional endpoints (1.0 = fully effective; 0 = absent). The neuroprotection window (blue), e.g., E2 efficacy against global cerebral ischemia injury, is fully open at 1 week post-OVX but closes by ~10 weeks, coinciding with ChIP-mediated ERα degradation and loss of local hippocampal E2 synthesis.[102,103] The synaptic plasticity window (amber), e.g., E2-induced enhancements in LTP, GluN2B-mediated NMDAR current, spine density, and novel object recognition, remains intact at 15 months post-OVX but closes between 15 and 19 months in aged Fischer 344 rats.[109–111] The dashed green line shows that initiating chronic low-level E2 at 11 months extends the synaptic plasticity window to 19 months.[109] Window closure is driven by deprivation duration, not chronological age: rats OVX'd at 20 months remain fully E2-responsive 1 month later.[109] Shaded zones indicate window status: both open (0 to ~10 weeks); neuroprotection closed only (~10 weeks–15 months); synaptic plasticity closing (15–19 months); both closed (≥19 months).

Curves are schematic representations of the direction and approximate timing of changes reported across the cited studies rather than pooled quantitative estimates. Where studies did not report identical time points, intermediate values were interpolated solely to illustrate the overall trajectory. All data from female rodent OVX models.

atrophy, small vessel disease burden, and WM integrity.[97] Together, these early studies suggest that menopause-related endocrine aging is accompanied by proteomic changes that overlap with pathways involved in neurodegeneration, although their reproducibility and clinical significance remain to be established.

Together, these data suggest that the menopausal transition is associated with a measurable neurobiological signature oriented toward the AD vulnerability pattern years before clinical symptoms emerge. Studies with larger samples and longer follow-up are needed to clarify the temporal dynamics and prognostic value of these alterations and to refine which combinations of endocrine, imaging, fluid, and symptom-based markers most accurately identify women on trajectories of elevated risk.

THE WINDOW OF OPPORTUNITY

The neuroendocrine lifespan suggests that hormone-sensitive brain remodeling unfolds within transition-specific temporal windows. Puberty initiates neurodevelopmental changes that extend through adolescence before reaching a more stable adult baseline, while pregnancy induces structural and functional remodeling that appears to follow a bounded postpartum trajectory rather than continuing indefinitely. These precedents support the view that the menopausal transition may likewise have its own neurobiological dynamics, with a potentially time-limited period of heightened plasticity and vulnerability during which interventions may align with the brain's adaptive responses. From this perspective, the hypothesized "window of opportunity" for neuroprotection may follow the time course of the underlying brain transition, rather than being defined solely by chronological age or years since the FMP.

The concept of a neurological window of opportunity or "timing hypothesis"[98,99] is anchored in preclinical models. The preclinical literature suggests that brain ER expression is dynamically regulated in a region-specific, receptor-specific, and time-dependent trajectory. Early increases in ER expression can be detected after ovariectomy, including upregulation of ERα mRNA in hypothalamic nuclei within 72 h[100] and increased hippocampal ERα protein by approximately 2 weeks.[101] This is consistent with a transient compensatory response to acute ligand withdrawal. With more sustained estrogen deprivation, the dominant pattern is progressive receptor loss: hippocampal ERα is reduced after ~10 weeks of ovariectomy in association with chromatin immunoprecipitation (ChIP)-mediated ubiquitination and proteasomal degradation,[102] with sustained declines across multiple brain regions over 4–12 weeks and beyond.[103] Although more work is needed, as shown in Figure 3, the core pattern is a biphasic response: an early days-to-weeks phase of transient ERα upregulation or maintenance, followed by progressive ERα depletion with longer estrogen deprivation, especially beyond about 10 weeks. Loss of responsiveness reflects not just falling ovarian E2 but depletion of the receptor substrate itself, compounded by loss of local E2 synthesis.[103] However, these trajectories seem to be region- and ER-dependent, with ERα increasing in some forebrain regions while declining in others, whereas ERβ shows a more consistent progressive decrease across several regions[104–107] (Figure 3).

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Critically, preclinical evidence indicates that the timeline for intervention is not a single threshold but likely a hierarchy of endpoint-specific sub-windows that close on different timescales (Figure 3). E2 treatment for acute ischemic injury—a proxy for neuroprotection—is fully effective at 1 week post-ovariectomy but ineffective by ~10 weeks, coinciding with ChIP-mediated ERα depletion and loss of local hippocampal E2 synthesis.[102,103] In contrast, E2-driven hippocampal synaptic plasticity—including enhancements in LTP, GluN2B-mediated NMDA receptor transmission, dendritic spine density, and object recognition memory—remains intact up to 15 months post-ovariectomy in aged rodents before closing between 15 and 19 months.[109–111] This later window can be extended by initiating chronic low-level E2 replacement by 11 months post-ovariectomy,[109] and its closure reflects deprivation duration rather than chronological age, as animals ovariectomized at the same age but with shorter deprivation remain fully E2-responsive.[109] Thus, different estrogen-mediated brain functions surrender their hormonal responsiveness at different rates, likely reflecting differences in the ERα abundance threshold each function requires and in the degree to which ERβ and membrane-associated ER signaling can compensate for progressive nuclear ERα loss. Nevertheless, the animal literature indicates temporally dynamic but ultimately diminishing ER availability and signaling capacity in both reproductive and cognitive regions after permanent cessation of ovarian E2 production.

Translating this concept to humans, however, has proved challenging, partly because direct visualization and measurement of hormone action in the living brain remain largely beyond reach. Advances in-brain estrogen imaging, including PET-based approaches capable of quantifying regional ER availability or ligand binding, are needed to provide a biomarker of brain responsiveness to estrogen—one that can help define when the window opens, how long it remains active, and when it begins to close. Although evidence in humans is very limited, *in vivo* 18F-fluoroestradiol (18F-FES) PET studies in healthy midlife women aged 40–65 showed progressively higher ER density in the pituitary gland and additional ER-regulated regions across the menopause transition, independent of age and circulating E2.[112,113] ER density remained elevated at 65, suggesting that some brain regions may remain responsive to estrogen longer than previously assumed, although this remains to be confirmed in larger and longitudinal studies, as well as with higher-affinity ligands.

So far, the strongest evidence that menopause may mark a peak in women's neurological vulnerability comes from neuroimaging and biomarker studies of menopausal staging. As discussed above, prospective studies, especially those tracking progression from one menopause stage to another in the same women, will be key to defining the temporal dynamics of brain changes across the transition. Even so, available evidence suggests that early postmenopause and perimenopause are accompanied by measurable alterations in AD-related biomarkers that are distinct from patterns observed in premenopause and age-controlled men.[66–81] This supports investigation of menopause as a biologically sensitive phase of brain aging rather than a simple correlate of later-life neurodegeneration. This timing framework has also motivated clinical interest in whether menopause hormone therapy (MHT) initiated near menopause can alter later brain aging trajectories. Three lines of evidence triangulate the timing hypothesis based on MHT findings.

Randomized controlled clinical trials of older postmenopausal women

First, the Women's Health Initiative Memory Study (WHIMS) remains the only randomized placebo-controlled trial to test MHT effects on dementia incidence. It enrolled women aged 65–79 and compared conjugated equine estrogens (CEE) alone in women with hysterectomy, or CEE plus medroxyprogesterone acetate (MPA) in women with an intact uterus, against placebo.[114,115] In this late-postmenopausal population, CEE/MPA therapy doubled dementia risk, while CEE alone showed a non-significant trend toward increased risk.[114,115] In both studies, the absolute increase in risk was, however, small (12 additional cases of dementia for 1,000 women using CEE/MPA for 5 years, and 6 additional cases per 1,000 women using CEE for 5 years). These findings, however, must be interpreted in context. WHIMS was a late-intervention study of older women, generally more than a decade past menopause and without active menopausal symptoms, so its results may not generalize to women initiating therapy in midlife.[114,115] AD was also not the primary endpoint, as the study shifted to all-cause dementia because fewer AD cases occurred than expected.[114,115] Interestingly, some analyses suggest that women who had used MHT before WHIMS enrollment—presumably closer to midlife—were less likely to develop dementia,[116] which warrants further investigation. Overall, WHIMS results are best read as evidence against late initiation of oral CEE/MPA rather than as a verdict on the timing hypothesis itself. These results cannot be generalized to other MHT regimens or patient populations. WHIMS tested only oral CEE with or without continuous oral MPA in women well past menopause, whereas contemporary clinical practice often uses more individualized regimens, including micronized E2 or progesterone started earlier to treat menopausal symptoms and different routes of administration.

Randomized controlled clinical trials of younger postmenopausal women

Second, subsequent large-scale randomized controlled trials (RCTs), including the WHIMS of younger women (WHIMS-Y), the Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog), and the Early versus Late-Intervention Trial with Estradiol–Cognitive Endpoints (ELITE-Cog), predominantly indicated preserved cognition without adverse effects,[117–120] supporting the cognitive safety of early initiation within the populations, formulations, and follow-up periods studied. To date, KEEPS provides the only RCT evidence linking estrogen therapy to brain Aβ burden. In a sub-study of 68 early postmenopausal women, Aβ PET imaging performed approximately 7 years after randomization and 3 years after treatment discontinuation showed lower brain Aβ burden in those assigned to transdermal 17β-estradiol (n = 21) compared with placebo (n = 30), but no effects of oral CEE (n = 17).[121] On stratification by APOE-4 genotype, these effects were driven by APOE-4 carriers, whereas no association was observed

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among non-carriers.[121] The transdermal estradiol group included a higher proportion of APOE-4 carriers than the oral CEE and placebo groups (50% vs. 18% and 18%, respectively), complicating interpretation of the treatment comparisons. However, this imbalance would be expected to bias toward greater rather than lower Aβ burden in the transdermal group.[121] These findings were not accompanied by differences in cognitive performance, indicating that the observed Aβ difference was not accompanied by a measurable cognitive benefit at the time of follow-up.[121] Route of administration may also be relevant. Oral estrogens undergo first-pass hepatic metabolism and exert greater effects on hepatic protein synthesis, coagulation factors, and lipid metabolism, whereas transdermal estradiol largely avoids first-pass metabolism and produces more stable circulating estradiol exposure.[2,122] However, evidence that these pharmacokinetic differences translate into differential effects on brain aging or AD risk remains limited.

Observational studies

Several cohorts, including Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE), Cache County, and Kaiser Permanente, found that MHT use in midlife was associated with lower risk of AD or all-cause dementia, whereas initiation in later life was neutral or associated with increased risk,[99,123,124] broadly echoing WHIMS. Although more recent observational studies have been mixed, meta-analytic evidence suggests that MHT initiated in midlife, and especially with estrogen-only therapy for women undergoing hysterectomy/oophorectomy, may be associated with lower risk of both AD and all-cause dementia, whereas late-life initiation may carry increased risk.[122,125–127] Interestingly, some observational studies report that postmenopausal MHT users exhibit smaller increments in plasma $A\beta_{42/40}$ (possibly reflecting less central Aβ deposition), with effects appearing more evident among APOE-4 carriers,[128] as well as lower tau-PET signal and lower CSF and plasma p-tau_{181} concentrations compared with non-users.[129] Incorporating AD biomarkers into ongoing research represents a strategic advance, as these outcomes may capture neurobiological effects of hormone exposure years before clinical endpoints such as cognitive decline or dementia incidence become detectable. This is particularly important in midlife cohorts, where absolute dementia risk is low and trials powered for clinical conversion are often impractical. Biomarker-based approaches may help resolve some of the long-standing inconsistencies in the MHT literature by providing a more proximal readout of target engagement and disease-relevant biology. This will make it possible to ask not only whether MHT affects AD and dementia risk in the aggregate but also whether specific regimens modify Aβ, tau, metabolism, neurovascular function, or synaptic integrity in the women most likely to benefit. However, biomarker effects should not be interpreted as evidence of clinical benefit unless linked prospectively to cognitive trajectories or dementia outcomes, and effects on cognition do not necessarily predict later dementia incidence.

Observational MHT findings require cautious interpretation. Women who initiate and continue MHT may differ systematically from non-users in education, socioeconomic status, health behaviors, access to care, and baseline health, introducing healthy-user and survivor biases.[122] Results may also be influenced by indication bias, immortal-time bias, and confounding by reproductive history, particularly hysterectomy and oophorectomy, which may influence both treatment selection and underlying neurological risk. Comparisons are further complicated by substantial heterogeneity in age and timing of initiation, formulation, dose, route of administration, duration of use, and progestogen type.[122,125–127] Accordingly, observational associations cannot establish that MHT itself reduces or increases AD risk, even when analyses adjust for measured confounders.

CONCLUSIONS AND FUTURE DIRECTIONS: TOWARD PRECISION CARE

The central argument of this review is that AD risk in women reflects the cumulative neurobiological effects of genetics, medical history, environmental and lifestyle influences and a lifelong ovarian-brain dialog reshaped across puberty, pregnancy, and perimenopause.[9,36,37] Although several risk factors are increasingly recognized in the AD prevention literature,[130] the specific contribution of neuroendocrine aging in general, and menopause in particular, has received disproportionately little attention relative to its potential biological impact. Redressing this imbalance is both a scientific and clinical priority. If the brain is being shaped—and in some women primed for vulnerability—by hormonal biology from adolescence onward, then interventions calibrated to the late-postmenopausal or prodromal AD stage may arrive too late. The field has spent 30 years studying the aging brain after the midlife transition; it now needs to define what happens during it.

The evidence reviewed here converges on a clinically relevant hypothesis: the menopausal transition may not be merely a reproductive endpoint but a neuroendocrine inflection point with potential relevance to AD risk. The biological case for examining whether intervention during this window represents a valuable prevention strategy rests on three pillars: (1) preclinical evidence that E2 replacement is neuroprotective only when initiated proximate to ovarian hormone loss; (2) the presence of AD-biomarker endophenotypes at the early postmenopausal and perimenopausal stages, although most available human studies are cross-sectional and cannot fully separate menopause-related effects from chronological aging; and (3) emerging but still conflicting evidence that early-initiation MHT—unlike late initiation—may be associated with reduced AD and dementia risk in at least some women, particularly those experiencing premenopausal oophorectomy.

Several questions now define the agenda for the field. First, does the menopausal biomarker shift (↑Aβ, ↑p-tau, ↓CMRglc, ↓structural integrity) represent a transient state that later stabilizes, or do its severity and duration influence downstream AD trajectories? Addressing this will require longitudinal biomarker studies beginning in late premenopause and extending at least a decade into postmenopause. Second, what is the cellular basis of the timing hypothesis—how does a relatively brief delay in E2 replacement close the window of responsiveness? Several neuroendocrine mechanisms appear to recur across the reproductive lifespan, including kisspeptin-GnRH signaling, estrogen-sensitive bioenergetic and synaptic pathways, and

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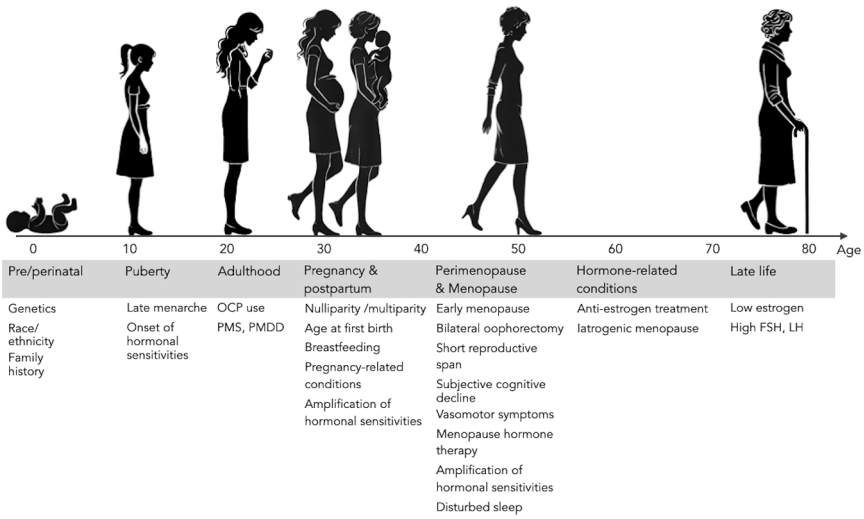


Figure 4. Female life-course factors relevant to aging and Alzheimer's risk

Conceptual framework illustrating reproductive, hormonal, and clinical exposures across the female lifespan that may modify later brain aging and AD vulnerability. Listed factors are examples of potentially cumulative or interacting influences and are not all established causal determinants.

neurosteroid-related affective circuitry, suggesting that menopause may represent the final expression of a longer pattern of hormone-sensitive brain remodeling. Answering this may identify alternative molecular targets that remain actionable after the hormonal timeline has narrowed and better anchoring of translational clinical research into mechanistic findings. Third, how do different MHT formulations, routes of administration, and combination regimens map onto neuroprotective, neutral, or adverse outcomes across individual biological profiles? Preclinical data suggest potential distinctions for micronized E2 versus CEEs, transdermal versus oral delivery, and micronized progesterone versus progestins, but these differences have not been tested head-to-head in adequately powered trials.

A central bottleneck is the absence of sensitive, validated endpoints capable of detecting early neuroprotection before clinical decline becomes measurable. Future studies and trials will benefit from biomarker-defined enrollment criteria—prioritizing women with subclinical metabolic or Aβ/tau signal—and multimodal biomarker composites as co-primary endpoints alongside cognitive measures so that intervention effects can be detected within realistic trial durations. A particularly important unmet need is direct imaging of estrogen signaling in the living brain. Current prevention trials rely on downstream readouts—cognition, structural MRI, Aβ/tau biomarkers—but none directly measures the neuroendocrine substrate that menopause and MHT are presumed to modify. Brain ER imaging, as well as imaging of other hormone receptors, will be pivotal to obtaining a direct readout of neuroendocrine aging *in vivo* and helping to define which women retain an estrogen-responsive substrate amenable to intervention.[112,113] Such tools are also needed to distinguish women who are biologically likely to benefit from hormonal intervention from those in whom the estrogen-responsive substrate has already diminished and would substantially strengthen the design of precision-medicine trials.

Although the role of MHT for AD prevention remains under investigation, the emerging picture supports evaluating intervention timing and administration by reproductive history (spontaneous vs. induced menopause and age at FMP), symptom burden, genetic risk, and biomarker profile. Women at the highest biological risk are both the population most likely to benefit from biologically informed prevention strategies and the population most underrepresented in trials. Just as importantly, perimenopause itself remains incompletely recognized as a stage warranting neurological attention and is still rarely operationalized in human studies as an intervention window. Testing the prevention potential of this window will require moving from the binary question of whether MHT is harmful or not toward a more precise one: for whom, when, with what formulation, and monitored with which biomarkers, can MHT alter the trajectory toward AD? Non-estrogenic pathways may also broaden the therapeutic landscape beyond MHT, including modulation of progesterone-allopregnanolone signaling, neurokinin pathways, and gonadotropin-related mechanisms. To date, their relevance to brain aging and AD prevention remains largely untested.

Not all women experience menopause with equivalent vulnerability, and personalizing the risk conversation will require attention to several intersecting factors. A life-course perspective on female-specific reproductive and endocrine factors that may shape later AD vulnerability is summarized in Figure 4. As reviewed above, early menopause, particularly when due to PO/BSO, is associated with increased AD and dementia risk and should prompt earlier risk assessment. APOE-4 genotype represents an additional amplifier, as women who are APOE-4 carriers show higher risk and more pronounced elevations in postmenopausal AD pathophysiology than genotype-matched men,[131] suggesting a genotype-by-sex-by-menopause interaction that remains inadequately characterized. Emerging data also position frequent VMS as both symptoms to treat and markers of neuroendocrine instability that may warrant closer surveillance. Similar attention is warranted for menopause-related and, more broadly, midlife SCD and forgetfulness, which could serve as early clinical stress tests of vulnerability to later cognitive impairment.

More broadly, the neuroendocrine aging framework articulated here remains largely absent from current AD prevention guidelines, trial designs, and clinical training. Menopause history is rarely collected in AD cohorts; ovarian age is not routinely assessed in at-risk women; and the concept of a hormonal sensitivity window has not been operationalized in prevention studies. Changing this will require integration across disciplines that do not yet routinely work together—neurology, radiology, reproductive endocrinology, gynecology, and precision medicine.

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Women's midlife is not simply a switch between reproductive and non-reproductive function. It is a neurologically active period during which processes relevant to later-life brain aging and AD vulnerability may begin to emerge. The task ahead is to systematically define these processes and determine whether and how they can inform risk stratification and prevention research.

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DECLARATION OF INTERESTS

The author declares no competing interests.

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