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MENOPAUSAL HORMONE THERAPY AND DEMENTIA RISK: AN INTEGRATED NEUROVASCULAR AND PRECISION MEDICINE PERSPECTIVE

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ABSTRACT

Background: The relationship between menopausal hormone therapy (MHT) and dementia risk remains controversial. Early observational studies suggested neuroprotective effects, whereas large randomized trials reported neutral or adverse outcomes in older women. These inconsistencies led to the development of the therapeutic window hypothesis, proposing that cognitive effects depend on the timing of therapy initiation relative to menopause onset.
Objective: This narrative review aims to critically synthesize contemporary evidence (1990–2025) regarding the association between MHT and dementia risk, integrating randomized controlled trials, longitudinal cohort studies, neuroimaging findings, and mechanistic data within a broader neurovascular and precision medicine framework.
Methods: A structured narrative approach was employed to evaluate major clinical trials, epidemiological cohorts, and translational research examining timing of initiation, formulation type, route of administration, vascular risk burden, and genetic modifiers such as APOE genotype.
Results: Evidence suggests that initiation of MHT within approximately five years of menopause appears cognitively neutral and may confer modest benefit in selected populations, particularly in the absence of significant cerebrovascular pathology. In contrast, initiation after age 65 or following prolonged hypoestrogenism is associated with increased dementia risk in some randomized trials. Emerging data indicate that formulation, progestogen type, cardiometabolic status, and genetic background modify cognitive trajectories.
Conclusions: Current evidence does not support the use of MHT solely for dementia prevention. However, timing and individual risk profiles substantially influence risk–benefit ratios. A precision medicine approach integrating neurovascular health and genetic susceptibility may better explain heterogeneity in observed outcomes and guide individualized clinical decision-making.

KEYWORDS

Hormone Replacement Therapy (MeSH), Menopause, Dementia, Alzheimer Disease, Cognition, Cerebrovascular Disorders

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1. Introduction

Dementia represents one of the most pressing public health challenges of the 21st century, with Alzheimer's disease accounting for the majority of cases worldwide. Notably, women constitute nearly two-thirds of individuals living with Alzheimer's disease, a disparity that cannot be fully explained by differences in life expectancy alone (Mielke et al., 2014; Nebel et al., 2018). While increased longevity contributes to higher prevalence rates among women, accumulating evidence suggests that biological sex–specific factors, including hormonal transitions, may play a critical role in modulating neurodegenerative risk trajectories (Nebel et al., 2018; Snyder et al., 2016). Among these factors, menopause has emerged as a potential inflection point in female brain aging.

Menopause is characterized by the permanent cessation of ovarian follicular activity and a profound decline in circulating estradiol levels (Brinton et al.,2015). Beyond its reproductive function, estradiol exerts pleiotropic effects on the central nervous system, influencing synaptic plasticity, cerebral glucose metabolism, mitochondrial function, and neuroimmune regulation (Arevalo et al.,2015; Brinton, 2009; Frick et al.,2015; Gibbs, 2010). During the menopausal transition, fluctuations followed by sustained reduction in estrogen availability are associated with vasomotor symptoms, sleep disturbances, and subjective cognitive complaints, particularly affecting attention and verbal memory (Maki & Henderson, 2016). Neuroimaging studies have demonstrated metabolic and structural changes in brain regions critical for memory processing, including the hippocampus and posterior cingulate cortex, during the perimenopausal and early postmenopausal stages

(Bean et al., 2014; Daniel, 2013; Mosconi et al., 2017). These findings have prompted renewed interest in the hypothesis that estrogen depletion may contribute to long-term vulnerability to neurodegenerative disease (Brinton, 2009; Mosconi et al., 2017).

The potential relationship between menopausal hormone therapy (MHT) and dementia risk has been debated for more than three decades (Henderson, 2014; Sherwin, 2003). Observational studies conducted in the 1990s suggested that women who used hormone therapy exhibited a reduced incidence of Alzheimer's disease compared with non-users (Tang et al., 1996; Yaffe et al., 1998). These early findings were widely interpreted as evidence of estrogen-mediated neuroprotection (Rocca et al., 2007; Yaffe et al., 1998). However, the publication of large randomized controlled trials, most notably the Women's Health Initiative and its cognitive substudy, challenged this assumption (Manson et al., 2013; Rapp et al., 2003; Shumaker et al., 2004). In women aged 65 years and older who initiated combined estrogen–progestin therapy, an increased incidence of probable dementia was observed, leading to substantial re-evaluation of the risk–benefit profile of hormone therapy (Rapp et al., 2003; Shumaker et al., 2004).

The apparent discrepancy between observational and randomized evidence gave rise to the so-called "therapeutic window" or "critical window" hypothesis (Maki, 2013; Whitmer et al., 2011). This concept proposes that the neural effects of estrogen are temporally dependent, such that initiation of therapy near the onset of menopause may confer neutral or even beneficial cognitive effects, whereas initiation after prolonged hypoestrogenism may be ineffective or potentially harmful. Biological plausibility for this hypothesis derives from experimental models demonstrating that sustained estrogen deprivation can alter receptor expression, intracellular signaling pathways, and cerebrovascular responsiveness, thereby limiting the restorative capacity of late hormone exposure (Brinton, 2009; Resnick et al., 2018).

Although the therapeutic window hypothesis has provided a useful conceptual framework, it may represent an oversimplification of a complex, multidimensional process. Emerging evidence indicates that cognitive outcomes associated with MHT are influenced not only by timing but also by formulation (e.g., conjugated equine estrogens versus 17β-estradiol), route of administration (oral versus transdermal), type of progestogen, baseline cerebrovascular health, cardiometabolic risk burden, and genetic susceptibility, particularly apolipoprotein E (APOE) genotype (Henderson et al., 2016; Hodis et al., 2016; Scott et al., 2012). Furthermore, advances in neuroimaging and biomarker research have revealed dynamic interactions between estrogen status, brain metabolism, and vascular aging, suggesting that a purely chronological definition of "early" versus "late" initiation may be insufficient (Mosconi et al., 2017; Mosconi et al., 2018).

In this context, a broader integrative perspective is warranted. Rather than viewing timing as an isolated determinant, it may be more appropriate to conceptualize the relationship between MHT and dementia risk within a neurovascular and precision medicine framework (Apostolakis & Doumas, 2013; Hodis et al., 2016; Maki & Henderson, 2016). Such an approach considers endocrine transition, vascular integrity, metabolic health, and genetic background as interdependent modifiers of cognitive trajectories in aging women.

The aim of this narrative review is therefore to critically synthesize contemporary evidence regarding the association between menopausal hormone therapy and dementia risk, integrating randomized trials, observational cohorts, neuroimaging findings, and mechanistic research. By re-examining the therapeutic window hypothesis through an interdisciplinary lens (Maki, 2013; Whitmer et al., 2011), this review seeks to clarify areas of consensus and controversy, identify methodological limitations in the current literature, and propose a conceptual model that may better account for heterogeneity in observed outcomes. Ultimately, a refined understanding of these interactions is essential to inform individualized clinical decision-making and future research directions in women's brain health.

2. Methodology

This article was designed as a structured narrative review aimed at critically examining the association between menopausal hormone therapy (MHT) and dementia risk within a translational and precision medicine framework. Although not conducted as a formal systematic review or meta-analysis, the literature synthesis followed predefined conceptual domains to ensure methodological transparency and thematic coherence.

2.1. Literature Scope and Search Strategy

The review focused on peer-reviewed publications published between January 1990 and March 2025. Particular emphasis was placed on contemporary evidence from 2002 onward, following the publication of the Women's Health Initiative (WHI) trials (Rapp et al., 2003; Shumaker et al., 2004), which substantially influenced clinical perspectives on hormone therapy and cognitive risk.

Electronic databases commonly used in biomedical research, including PubMed/MEDLINE and Scopus-indexed journals, were consulted to identify relevant literature. Search terms included combinations of the following keywords: menopausal hormone therapy, hormone replacement therapy, estrogen, dementia, Alzheimer's disease, cognition, therapeutic window, APOE, neuroimaging, and cerebrovascular disease. Reference lists of key articles and major narrative reviews were also manually screened to identify additional relevant publications (Maki, 2013; Maki & Henderson, 2016; Whitmer et al., 2011).

Priority was given to studies published after 2000, reflecting advances in neuroimaging, biomarker research, and mechanistic understanding of estrogen signaling in the aging brain (Mosconi et al., 2017; Snyder et al., 2016).

2.2. Study Selection Criteria

Studies were considered eligible for inclusion if they met one or more of the following criteria:

Randomized controlled trials evaluating cognitive outcomes or dementia incidence in women receiving MHT (Rapp et al., 2003; Shumaker et al., 2004; Henderson et al., 2016; Snyder et al., 2016).

Prospective cohort studies assessing the association between MHT exposure and incident dementia or mild cognitive impairment (Yaffe et al., 1998; Ryan et al., 2014; Whitmer et al., 2011).

Neuroimaging or biomarker studies examining structural, metabolic, or molecular correlates of estrogen exposure in postmenopausal women (Mosconi et al., 2017; Kantarci et al., 2016).

Experimental or translational studies providing mechanistic insights into estrogen effects on neurodegeneration, synaptic plasticity, or cerebrovascular regulation (Apostolakis & Doumas, 2013; Brinton, 2009).

Narrative reviews, meta-analyses, or large-scale observational investigations addressing timing of hormone therapy initiation, formulation differences, or genetic modifiers of dementia risk (Maki & Henderson, 2016; Nebel et al., 2018; Snyder et al., 2016).

Studies were excluded if they:

- focused exclusively on surgical menopause without broader applicability,
- lacked defined cognitive or dementia-related endpoints,
- were non-peer-reviewed publications or conference abstracts without full data,
- addressed hormone therapy in non-menopausal clinical contexts.

2.3. Conceptual Domains of Analysis

To enhance interpretative clarity, included evidence was organized into predefined domains:

- Biological mechanisms of estrogen action in the central nervous system (Brinton, 2009)
- Randomized controlled trial evidence (Rapp et al., 2003; Shumaker et al., 2004; Snyder et al., 2016)
- Observational and registry-based cohort data (Ryan et al., 2014; Whitmer et al., 2011; Yaffe et al., 1998)
- Neuroimaging and biomarker studies (Kantarci et al., 2016; Mosconi et al., 2017)
- Neurovascular interactions and cardiometabolic modifiers (Apostolakis & Doumas, 2013; Hodis et al., 2016)
- Formulation-specific and pharmacological effects (Henderson et al., 2016; Hodis et al., 2016)
- Genetic and precision medicine considerations (Nebel et al., 2018; Snyder et al., 2016)

This domain-based framework allowed integration of heterogeneous evidence sources while maintaining thematic continuity aligned with the proposed neurovascular–precision model.

2.4. Approach to Evidence Interpretation

Given the heterogeneity of study designs, populations, hormone formulations, and cognitive endpoints, findings were synthesized qualitatively rather than quantitatively pooled. Particular attention was paid to several factors known to influence cognitive outcomes associated with menopausal hormone therapy:

- Age at therapy initiation (Whitmer et al., 2011)
- Time since menopause (Hodis et al., 2016)
- Duration of hormone exposure
- Type and route of estrogen administration (Henderson et al., 2016)
- Concomitant progestogen use (Rapp et al., 2003)
- Baseline vascular and metabolic risk factors (Apostolakis & Doumas, 2013)

- Genetic susceptibility markers, particularly the apolipoprotein E (APOE) genotype (Snyder et al., 2016; Nebel et al., 2018)

Contradictory findings across studies were examined in the context of methodological differences, including study power, follow-up duration, population age distribution, and heterogeneity in cognitive outcome definitions (Maki & Henderson, 2016).

2.5. Limitations of the Narrative Approach

As a narrative review, this synthesis does not provide a formal risk-of-bias assessment or statistical meta-analytic estimates. Selection bias cannot be entirely excluded, and conclusions rely on critical appraisal rather than quantitative aggregation. Nevertheless, the structured domain-based methodology was designed to minimize interpretative bias and to provide a comprehensive and clinically relevant overview of current knowledge regarding the relationship between menopausal hormone therapy and dementia risk.

3. Results

3.1. Biological Mechanisms Linking Estrogen and Neurodegeneration

Experimental and translational evidence consistently demonstrates that estradiol exerts multifaceted effects on central nervous system structure and function (Brinton, 2009; Maki, 2013). Estrogen receptors (ERα, ERβ, and membrane-associated G protein–coupled estrogen receptors) are widely expressed in brain regions critical for memory and executive function, including the hippocampus, prefrontal cortex, and amygdala (Brinton, 2009; Nebel et al., 2018). Activation of these receptors modulates synaptic plasticity through regulation of dendritic spine density, long-term potentiation, and neurotrophin signaling, particularly brain-derived neurotrophic factor (BDNF) (Brinton, 2009; Maki & Henderson, 2016).

In addition to synaptic regulation, estradiol influences mitochondrial bioenergetics and cerebral glucose metabolism (Brinton, 2009; Mosconi et al., 2017). Preclinical models suggest that sustained estrogen deprivation may impair mitochondrial efficiency and reduce metabolic flexibility, potentially increasing vulnerability to neurodegenerative processes (Brinton, 2009; Maki, 2013). Neuroinflammatory pathways are similarly modulated by estrogen, with evidence indicating attenuation of microglial activation and pro-inflammatory cytokine release under physiological estrogen exposure (Brinton, 2009; Nebel et al., 2018).

Importantly, experimental data indicate that the duration of estrogen deprivation may alter receptor expression and downstream signaling responsiveness. Prolonged hypoestrogenism has been associated with reduced receptor density and diminished intracellular signaling capacity, providing mechanistic plausibility for a time-dependent effect of hormone therapy initiation (Brinton, 2009; Maki & Henderson, 2016). These findings form the biological foundation of the therapeutic window hypothesis (Whitmer et al., 2011).

3.2. Evidence from Randomized Controlled Trials

Randomized controlled trials provide the most robust evidence regarding causality but have yielded heterogeneous findings. The Women's Health Initiative Memory Study (WHIMS), which enrolled women aged 65 years and older initiating combined estrogen–progestin therapy, reported an increased incidence of probable dementia compared with placebo (Shumaker et al., 2004). These findings were consistent with earlier analyses from the Women's Health Initiative trial evaluating cognitive outcomes in older postmenopausal women (Espeland et al., 2004; Rapp et al., 2003; Shumaker et al., 2004). Together, these results substantially altered clinical perceptions of hormone therapy and led to increased caution regarding late-life initiation of menopausal hormone therapy (Maki & Henderson, 2016; Whitmer et al., 2011).

However, subsequent trials enrolling younger, recently postmenopausal women demonstrated different outcomes. The Kronos Early Estrogen Prevention Study (KEEPS), which included women within three years of menopause, did not show significant adverse cognitive effects over the intervention period (Henderson et al., 2016). Similarly, the Early versus Late Intervention Trial with Estradiol (ELITE), which stratified participants based on time since menopause, demonstrated vascular benefits among early initiators and did not identify significant cognitive harm during the trial period (Hodis et al., 2016; Maki & Henderson, 2016).

Meta-analyses integrating randomized data suggest that initiation of menopausal hormone therapy after age 65 may be associated with increased dementia risk, whereas initiation closer to menopause appears largely cognitively neutral (Maki & Henderson, 2016; Whitmer et al., 2011). Importantly, most randomized trials were not powered with incident dementia as a primary endpoint and were limited by relatively short durations of cognitive follow-up, which restricts definitive conclusions regarding long-term neuroprotective effects (Maki & Henderson, 2016; Snyder et al., 2016).

3.3. Evidence from Observational Cohort Studies

Large prospective cohort studies have frequently reported a reduced risk of Alzheimer's disease among women who initiated menopausal hormone therapy near the onset of menopause (Ryan et al., 2014; Yaffe et al., 1998). These findings initially supported the hypothesis that estrogen exposure during the early postmenopausal period may exert neuroprotective effects.

However, interpretation of observational findings requires caution. Hormone therapy users often differ systematically from non-users in socioeconomic status, educational attainment, health behaviors, and healthcare utilization, a phenomenon commonly described as the healthy-user bias (Whitmer et al., 2011). Such differences may partially account for the apparent protective associations observed in early epidemiological studies.

More recent registry-based and population-level cohort analyses have produced heterogeneous results. Some investigations continue to report a modest reduction in dementia risk among women who initiate hormone therapy near menopause, whereas others observe no statistically significant association after rigorous adjustment for confounding variables (Maki & Henderson, 2016; Ryan et al., 2014). Duration of exposure and formulation of hormone therapy have also been proposed as potential effect modifiers, although evidence remains inconsistent (Whitmer et al., 2011).

Taken together, observational data suggest that early initiation of hormone therapy is unlikely to substantially increase dementia risk and may be associated with neutral or modestly beneficial cognitive outcomes. Nevertheless, residual confounding and methodological heterogeneity limit the ability of cohort studies to establish a causal neuroprotective effect (Maki & Henderson, 2016).

3.4. Neuroimaging and Biomarker Findings

Advances in neuroimaging have provided important insight into potential mechanistic correlates of estrogen exposure and brain aging in women (Mosconi et al., 2017; Mosconi et al., 2018). Structural magnetic resonance imaging (MRI) studies have reported associations between early menopausal hormone therapy use and preservation of hippocampal and cortical volumes in some cohorts, although findings remain heterogeneous across populations and study designs (Kantarci et al., 2016).

Functional imaging studies, including fluorodeoxyglucose positron emission tomography (FDG-PET), suggest that estrogen exposure may modulate cerebral glucose metabolism during the menopausal transition (Mosconi et al., 2017). Women initiating hormone therapy earlier in the postmenopausal period have demonstrated metabolic activity patterns resembling those observed in younger women, whereas prolonged estrogen deprivation has been associated with reduced metabolic efficiency in brain regions particularly vulnerable to Alzheimer's disease pathology (Mosconi et al., 2017; Mosconi et al., 2018).

Evidence from amyloid and tau positron emission tomography remains limited but suggests potential interactions between estrogen exposure and Alzheimer-related biomarker trajectories. Preliminary findings indicate that transdermal 17β-estradiol therapy may be associated with lower amyloid-β deposition in early postmenopausal women, particularly among carriers of the APOE ε4 allele (Kantarci et al., 2016). However, longitudinal studies linking hormone exposure, biomarker progression, and clinically confirmed dementia outcomes remain sparse (Resnick et al., 2018; Snyder et al., 2016).

3.5. Neurovascular and Cardiometabolic Modifiers

The interaction between estrogen status and vascular health represents a critical dimension in understanding dementia risk in postmenopausal women (Apostolakis & Doumas, 2013; Hodis et al., 2016). Estrogen enhances endothelial nitric oxide production, promotes vasodilation, and exerts anti-inflammatory effects within the vascular system. These protective mechanisms may attenuate with advancing age and increasing vascular stiffness, potentially altering the physiological response to hormone therapy (Apostolakis & Doumas, 2013).

Initiation of hormone therapy in the presence of established atherosclerosis or endothelial dysfunction may therefore produce different outcomes compared with initiation during periods of relatively preserved vascular integrity. Evidence from the Early versus Late Intervention Trial with Estradiol (ELITE) supports the concept that vascular responses to estradiol differ according to time since menopause (Hodis et al., 2016).

Cardiometabolic risk factors—including hypertension, obesity, insulin resistance, and dyslipidemia—are independently associated with cognitive decline and dementia (Mielke et al., 2014). Emerging evidence suggests that these factors may modify the cognitive impact of hormone therapy and contribute to the heterogeneity observed across clinical studies (Hodis et al., 2016; Maki & Henderson, 2016). Women with lower baseline vascular risk appear more likely to exhibit neutral or potentially favorable cognitive trajectories with early therapy initiation, whereas those with substantial vascular burden may derive limited benefit.

3.6. Influence of Formulation and Route of Administration

Differences in estrogen formulation and route of administration may contribute to divergent clinical outcomes observed across studies of menopausal hormone therapy (Hodis et al., 2016; Maki & Henderson, 2016). Conjugated equine estrogens and 17β-estradiol differ in receptor affinity, downstream signaling effects, and metabolic profiles, which may influence their impact on neural and vascular tissues (Brinton, 2009).

Route of administration represents an additional consideration. Transdermal estrogen delivery bypasses hepatic first-pass metabolism and may exert more stable effects on coagulation pathways, inflammatory markers, and lipid metabolism compared with oral formulations (Apostolakis & Doumas, 2013; Hodis et al., 2016). These pharmacokinetic differences may have implications for both vascular and neurological outcomes.

Progestogen type also appears to play a relevant role. Synthetic progestins such as medroxyprogesterone acetate may differ from micronized progesterone in their neurobiological and vascular effects (Brinton, 2009; Rapp et al., 2003). Experimental data further suggest that certain hormone combinations may differentially influence Alzheimer-like neuropathology, although clinical evidence remains limited (Scott et al., 2012). Comparative cognitive outcome data across formulations remain scarce, highlighting the need for future randomized trials addressing formulation-specific effects (Maki & Henderson, 2016).

3.7. Genetic and Precision Medicine Considerations

Genetic susceptibility plays a significant role in dementia risk independently of hormone exposure. The apolipoprotein E (APOE) ε4 allele is the strongest common genetic risk factor for late-onset Alzheimer's disease and is associated with increased amyloid accumulation, earlier disease onset, and accelerated cognitive decline (Mielke et al., 2014; Snyder et al., 2016). Experimental and clinical studies suggest that APOE genotype may also interact with hormonal status and estrogen signaling pathways in the brain (Resnick et al., 2018).

Emerging evidence indicates potential interactions between APOE genotype and the timing of menopausal hormone therapy initiation. Some observational analyses suggest that women carrying the APOE ε4 allele may exhibit different cognitive responses to hormone therapy compared with non-carriers, although findings remain inconsistent across studies (Snyder et al., 2016; Whitmer et al., 2011). These discrepancies likely reflect differences in study design, population characteristics, and hormone formulations.

The growing emphasis on precision medicine in neurodegenerative disease research highlights the importance of individualized risk assessment that incorporates genetic background, vascular health, metabolic status, and reproductive aging (Hodis et al., 2016; Resnick et al., 2018). Within this framework, menopausal hormone therapy may exert heterogeneous cognitive effects depending on the interaction between endocrine transition and underlying biological vulnerability. Consequently, integrating genetic markers such as APOE genotype with clinical and vascular risk profiles may help refine patient selection and improve the interpretation of divergent findings observed across studies (Whitmer et al., 2011; Snyder et al., 2016).

3.8. Synthesis of Findings

Collectively, the available evidence indicates that menopausal hormone therapy does not uniformly reduce dementia risk. Randomized controlled trials enrolling women aged 65 years and older initiating combined estrogen–progestin therapy have demonstrated an increased incidence of dementia compared with placebo, highlighting potential risks associated with late initiation (Rapp et al., 2003; Shumaker et al., 2004). Long-term follow-up analyses of the Women's Health Initiative further reinforced the complexity of the relationship between hormone therapy and neurological outcomes (Manson et al., 2013).

In contrast, studies examining women who initiated therapy closer to the menopausal transition have generally reported neutral cognitive effects, with some observational cohorts suggesting modest protective associations (Maki & Henderson, 2016; Ryan et al., 2014). Mechanistic and neuroimaging data also support the concept that estrogen exposure during the early postmenopausal period may influence brain metabolism and vascular function in ways that could affect long-term cognitive trajectories (Kantarci et al., 2016; Mosconi et al., 2017).

Taken together, these findings suggest that the relationship between menopausal hormone therapy and dementia risk cannot be explained solely by the timing of therapy initiation. Instead, cognitive outcomes appear to be influenced by complex interactions between endocrine factors, vascular health, metabolic status, hormone formulation, and genetic susceptibility (Apostolakis & Doumas, 2013; Hodis et al., 2016; Resnick et al., 2018). This multidimensional perspective supports the development of a neurovascular–precision medicine model, which may provide a more comprehensive framework for interpreting heterogeneous findings across clinical and epidemiological studies.

4. Discussion

4.1. Re-evaluating the Therapeutic Window Hypothesis

The therapeutic window hypothesis emerged as an attempt to reconcile discordant findings between early observational studies suggesting neuroprotection (Yaffe et al., 1998) and randomized trials demonstrating increased dementia risk with late initiation of menopausal hormone therapy (MHT) (Rapp et al., 2003; Shumaker et al., 2004). The central premise—that estrogen's neural effects are time-dependent and more favorable when therapy is initiated near menopause - remains biologically plausible (Brinton, 2009; Brinton et al., 2015) and partially supported by clinical data (Henderson et al., 2016; Resnick et al., 2018). However, the accumulated evidence suggests that timing alone is insufficient to explain the heterogeneity of cognitive outcomes (Whitmer et al., 2011).

Randomized data clearly indicate that initiation of MHT in women aged 65 years and older, particularly after prolonged hypoestrogenism, may increase dementia risk (Shumaker et al., 2004). Conversely, trials enrolling women closer to menopause have not demonstrated significant cognitive harm (Henderson et al., 2016), and some observational studies suggest possible benefit (Ryan et al., 2014). Yet, the magnitude of protective effects observed in observational research has not been replicated in randomized settings, raising concerns about residual confounding and healthy-user bias (Whitmer et al., 2011).

Thus, rather than confirming a simple early-benefit/late-harm dichotomy, the evidence supports a more nuanced interpretation: timing appears to be a necessary but not sufficient condition influencing cognitive trajectories (Maki & Henderson, 2016).

4.2. Biological Plausibility and Limits of the Timing Model

Preclinical models demonstrate that prolonged estrogen deprivation may alter receptor expression, mitochondrial efficiency, synaptic density, and cerebrovascular responsiveness (Arevalo et al., 2015; Brinton, 2009; Brinton et al., 2015). These findings provide mechanistic support for reduced efficacy—or potential harm—when estrogen therapy is initiated long after menopause. However, translating these mechanistic insights to human populations remains complex.

Human brain aging is influenced by cumulative vascular injury, metabolic dysregulation, systemic inflammation, and genetic susceptibility (Snyder et al., 2016). Estrogen signaling operates within this broader biological context (Apostolakis & Doumas, 2013). If neuronal networks have already undergone significant degenerative or vascular compromise, exogenous hormone exposure may not restore prior neuroprotective pathways. Conversely, in relatively preserved neural environments, early intervention may help maintain metabolic and synaptic resilience (Mosconi et al., 2017).

The therapeutic window hypothesis, therefore, may oversimplify a multifactorial biological reality by focusing primarily on chronological timing rather than neurobiological state (Whitmer et al., 2011).

4.3. Neurovascular Integrity as a Central Modifier

One of the most consistent themes emerging from recent evidence is the central role of vascular health (Apostolakis & Doumas, 2013; Hodis et al., 2016). Dementia pathophysiology is increasingly recognized as involving both neurodegenerative and cerebrovascular mechanisms (Mielke et al., 2014). Estrogen exerts vasodilatory, endothelial-supportive, and anti-inflammatory effects (Apostolakis & Doumas, 2013), but these benefits may depend on baseline vascular integrity.

In early postmenopause, when endothelial function may still be relatively preserved, estrogen exposure could support vascular homeostasis and cerebral perfusion (Hodis et al., 2016). In contrast, in the presence of established atherosclerosis, arterial stiffness, or microvascular disease, hormonal modulation may have diminished efficacy or potentially adverse effects.

This neurovascular perspective aligns with data showing that cardiometabolic risk factors—hypertension, obesity, diabetes, and dyslipidemia—modify dementia risk independently (Mielke et al., 2014). It is therefore plausible that the cognitive impact of MHT reflects interaction between endocrine timing and vascular substrate. Such a model explains why age-based cutoffs (e.g., <60 vs. ≥65 years) may inadequately capture true biological risk (Whitmer et al., 2011).

4.4. Formulation, Route, and Progestogen Effects

The original therapeutic window framework largely treated hormone therapy as a homogeneous exposure. However, differences in estrogen type, dose, and route of administration introduce important variability (Hodis et al., 2016).

Oral conjugated equine estrogens undergo hepatic first-pass metabolism, influencing coagulation and inflammatory pathways differently from transdermal 17β-estradiol (Apostolakis & Doumas, 2013). Likewise, synthetic progestins may differ substantially from micronized progesterone in terms of neurobiological and vascular effects (Brinton, 2009; Rapp et al., 2003). Some evidence suggests that medroxyprogesterone acetate may attenuate certain beneficial estrogen-mediated mechanisms observed with natural progesterone (Brinton, 2009; Scott et al., 2012).

Although definitive comparative cognitive trials remain limited, these formulation-specific differences suggest that the concept of a therapeutic window cannot be separated from pharmacological characteristics (Maki & Henderson, 2016). A therapy initiated early but using a less physiologically aligned formulation may not yield equivalent outcomes.

4.5. Genetic Susceptibility and Precision Medicine

The role of apolipoprotein E (APOE) genotype introduces another dimension to risk stratification. APOE ε4 carriers exhibit heightened vulnerability to Alzheimer's pathology, altered lipid metabolism, and differential neuroinflammatory responses (Resnick et al., 2018; Snyder et al., 2016). Emerging data suggest possible interactions between APOE genotype and estrogen exposure, although findings are inconsistent (Snyder et al., 2016; Whitmer et al., 2011).

Precision medicine approaches propose that therapeutic decisions should integrate genetic background, vascular status, metabolic profile, and menopausal timing (Hodis et al., 2016; Snyder et al., 2016). From this perspective, the therapeutic window may represent a population-level observation that obscures meaningful interindividual variability.

Future research should prioritize stratified analyses incorporating genetic and vascular biomarkers to determine whether specific subgroups derive differential cognitive effects from early hormone therapy (Maki & Henderson, 2016).

4.6. Clinical Implications

Current evidence does not support prescribing MHT solely for the purpose of dementia prevention (Maki & Henderson, 2016). Initiation after age 65, particularly in women with elevated vascular risk, should be approached cautiously given randomized evidence of increased dementia incidence in this population (Shumaker et al., 2004).

For symptomatic women in early menopause, cognitive neutrality appears the most consistent conclusion (Henderson et al., 2016). In carefully selected individuals with low vascular risk and no contraindications, MHT may be considered for approved indications (e.g., vasomotor symptom relief) without strong evidence of cognitive harm when initiated near menopause (Hodis et al., 2016).

Importantly, clinicians should avoid extrapolating early observational claims of neuroprotection to universal preventive recommendations (Whitmer et al., 2011).

4.7. Limitations of Current Evidence

Several methodological constraints limit definitive conclusions:

- Many randomized trials were not powered for dementia as a primary endpoint (Maki & Henderson, 2016).
- Follow-up durations may be insufficient to capture long-latency neurodegenerative outcomes (Henderson et al., 2016).
- Observational studies remain vulnerable to confounding by indication and healthy-user bias (Whitmer et al., 2011).
- Biomarker-confirmed Alzheimer's disease outcomes remain limited, although emerging neuroimaging studies during the menopausal transition are beginning to address this gap (Mosconi et al., 2017; Mosconi et al., 2018).
- Heterogeneity in formulations, dosing, and duration complicates direct comparison (Hodis et al., 2016).

These limitations reinforce the need for cautious interpretation and further targeted research.

4.8. Toward an Integrated Neurovascular–Precision Model

The cumulative evidence suggests that the therapeutic window hypothesis, while biologically grounded, is incomplete (Whitmer et al., 2011). A more comprehensive model integrates:

- Endocrine timing (age and time since menopause),
- Neurovascular integrity (Apostolakis & Doumas, 2013),
- Cardiometabolic burden (Mielke et al., 2014),
- Hormone formulation and route (Hodis et al., 2016),
- Genetic susceptibility (Snyder et al., 2016).

Within this multidimensional framework, timing is repositioned as one component of a broader biological matrix rather than a standalone determinant of dementia risk.

Such reconceptualization may better align clinical decision-making with individual patient characteristics and guide future randomized trials designed to test stratified interventions (Maki & Henderson, 2016).

5. Conclusions

The relationship between menopausal hormone therapy (MHT) and dementia risk remains complex and context-dependent. Over the past two decades, the therapeutic window hypothesis has provided a biologically plausible explanation for discrepant findings observed between observational studies and randomized controlled trials (Whitmer et al., 2011; Maki & Henderson, 2016). Evidence consistently indicates that initiation of MHT after the age of 65 years, particularly following prolonged estrogen deprivation, may increase the risk of dementia (Shumaker et al., 2004). In contrast, initiation near the menopausal transition appears cognitively neutral in randomized trials (Henderson et al., 2016) and has not demonstrated convincing long-term neuroprotective effects in controlled clinical settings (Maki & Henderson, 2016).

However, the accumulated data do not support a simplistic early-benefit versus late-harm dichotomy. Timing of initiation interacts with multiple modifying factors, including vascular health, cardiometabolic burden, hormone formulation, route of administration, and genetic susceptibility (Hodis et al., 2016; Snyder et al., 2016). The heterogeneity observed across clinical, epidemiological, and neuroimaging studies suggests that chronological age alone does not adequately capture biological vulnerability or resilience (Hodis et al., 2016; Mosconi et al., 2017).

Current evidence does not justify the use of MHT solely for the prevention of dementia (Maki & Henderson, 2016). Clinical decisions regarding hormone therapy should remain guided by established indications—primarily management of menopausal symptoms—while carefully considering individual cardiovascular and metabolic risk profiles (Apostolakis & Doumas, 2013; Hodis et al., 2016). In women initiating therapy near menopause, available data provide reassurance regarding cognitive safety (Henderson et al., 2016), but not definitive evidence of neuroprotection (Maki & Henderson, 2016).

Future research should prioritize biomarker-informed and genotype-stratified trials, with extended longitudinal follow-up and standardized cognitive endpoints (Snyder et al., 2016; Mosconi et al., 2017). Integrating endocrine timing with neurovascular and precision medicine frameworks may offer a more accurate conceptual model for understanding dementia risk in women (Hodis et al., 2016; Snyder et al., 2016).

In conclusion, the therapeutic window hypothesis remains a valuable heuristic model (Whitmer et al., 2011), but its explanatory power is enhanced when embedded within a multidimensional neurovascular–precision framework (Hodis et al., 2016; Snyder et al., 2016). Refining this integrative approach is essential for advancing individualized strategies in women's brain health and for clarifying the role of menopausal hormone therapy in long-term cognitive outcomes.

Conflict of Interest: The authors declare no conflict of interest.

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