

Sex-specific reproductive and hormonal factors in relation to Alzheimer's disease-related biomarkers: A Systematic Review

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Abstract

Objective: To systematically evaluate associations between female- and male-specific reproductive and hormonal factors and Alzheimer's disease (AD)-related biomarkers, identify consistently associated exposures, and assess differences across biomarker domains. The focus was on amyloid, tau, neurodegeneration, neuronal injury, cerebral metabolism, and cerebrovascular or white-matter biomarkers.

Methods: This systematic review was registered in PROSPERO (CRD420261363648). MEDLINE (Ovid), Embase, and Web of Science were searched from inception to 26 February 2026. Two reviewers independently screened studies, assessed eligibility, and extracted data. Studies examining reproductive factors, hormonal exposures including endogenous factors and exogenous factors, and reproductive endocrine disorders in relation to AD-related biomarkers were included. Risk of bias was assessed using the Newcastle-Ottawa Scale and the RoB2 tool.

Findings: Of 35,331 records identified, 101 studies met inclusion criteria, with most studies being judged as having a moderate risk or having some concern for bias. Evidence was strongest for female reproductive and hormonal factors. Menopausal transition and earlier menopause were associated with greater amyloid burden, reduced cerebral glucose metabolism, smaller global and regional brain volumes, cortical thinning, and poorer white-matter integrity in several studies. Higher follicle-stimulating hormone (FSH) concentrations were consistently associated with greater amyloid pathology in women. Hypertensive disorders of pregnancy, objectively measured nighttime vasomotor symptoms, and premenopausal bilateral oophorectomy were also linked to less favorable biomarker profiles. Associations were most evident in amyloid, neurodegeneration, and white-matter outcomes, whereas findings for tau pathology and neurofilament light were less consistent. Evidence regarding menopausal hormone therapy (MHT) was mixed; most longitudinal studies and randomized trials reported no clear associations with AD biomarkers, although some findings supported a potential critical-window effect, with more favorable outcomes when therapy was initiated near menopause. Evidence in men was sparse and insufficient to draw firm conclusions.

Conclusions: Menopausal status, age at menopause, and elevated FSH levels, showed more consistent associations with AD-related biomarkers than exogenous hormone exposures such as MHT. Menopause-related endocrine changes, earlier menopause, and selected female-specific reproductive health conditions may contribute to AD vulnerability, although longitudinal evidence remains limited and causal relationships cannot be established.

Introduction

Dementia is a major global health challenge,¹ and women account for nearly two-thirds of individuals affected by Alzheimer's disease (AD).² Although women's longer life expectancy contributes to this disparity, it does not fully explain the greater disease burden. Biological sex, reproductive aging, and

endogenous and exogenous hormone exposures may also influence susceptibility to AD and the development of AD pathology.^{3,4} Female reproductive events, including menarche, pregnancy, menopause, and hormone use, can provide important opportunities to investigate how endocrine changes across the life course may shape brain aging.

Previous meta-analyses have primarily examined clinical rather than biomarker outcomes. Melville et al. found no consistent evidence that menopausal hormone therapy (MHT) affects the risk of mild cognitive impairment (MCI) or dementia⁵, while Han et al. reported heterogeneous associations between sex-specific reproductive factors and cognitive decline or dementia.⁴ These findings provide clinical motivation to investigate endocrine changes, however, cognition and dementia are late and heterogeneous outcomes, and do not clarify the underlying mechanisms. Hallmark components of AD pathology, such as amyloid or tau pathology, along with other processes (e.g., neurodegeneration, cerebral metabolic dysfunction, cerebrovascular injury), are becoming increasingly relevant biomarkers to guide AD diagnosis and treatment and can help identify potential sex differences in responses to disease-modifying therapies.⁶

AD-related biomarkers allow disease processes to be examined before or alongside clinical impairment. Core biomarkers such as amyloid- β and tau measured using positron emission tomography (PET), cerebrospinal fluid (CSF), or blood-based assays,⁷ have only recently become of more interest in relation to sex-differences in AD pathology. Whereas other markers, such as hippocampal and cortical atrophy on magnetic resonance imaging (MRI) and altered cerebral glucose metabolism on fluorodeoxyglucose PET (FDG-PET), have been given more attention, as well as white matter hyperintensities (WMHs) and measures of white-matter (WM) integrity that may identify cerebrovascular pathways relevant to AD.⁸

Among women, biomarker studies have concentrated largely on menopause and MHT. Studies of age at menopause, reproductive history, premenopausal bilateral oophorectomy, and estrogen exposure have reported associations with hippocampal, medial temporal, or other brain volumes.^{9–15} Oral contraceptive use and MHT have sometimes been associated with preserved brain structure,^{14–17} whereas other studies have reported null or adverse associations and uncertain long-term effects.^{18–23} Evidence concerning reproductive lifespan and brain structure is also mixed.^{13,15,24} White-matter and cerebrovascular biomarkers are less frequently studied. Menopausal stage, reproductive lifespan, and reproductive hormones have been associated with variation in WMH burden or white-matter integrity, but findings remain limited and heterogeneous.^{25–27}

Evidence from functional and molecular biomarkers is similarly incomplete. Amyloid- β and tau have been examined in relation to menopause, endogenous hormone levels, reproductive lifespan, pregnancy-related factors, and MHT.^{20,21,25,28–40} Findings vary according to reproductive stage, hormone measurement, apolipoprotein (APOE) genotype, treatment timing and formulation, previous hormone exposure, and clinical status. FDG-PET studies suggest that cerebral glucose metabolism may change across the menopausal transition, particularly in AD-vulnerable regions.^{25,41–44} Estrogen exposure and

hormone therapy have been associated with regional metabolic differences, but their direction, timing, and persistence remain uncertain.^{14,44–47} Blood- and CSF-based biomarker studies are particularly scarce despite their growing importance.

Male reproductive and hormonal factors provide complementary evidence but have received little attention. Studies have focused mainly on testosterone, gonadotropins, and sex hormone-binding globulin, with limited research on hypogonadism, longitudinal androgen decline, gonadal conditions, or androgen-deprivation therapy.^{29,34,37,38,48–54} This evidence may help distinguish broader effects of gonadal aging from pathways more specific to female reproductive aging.

Overall, evidence on reproductive and hormonal factors and AD biomarkers remains fragmented across exposures, biomarker modalities, and stages of the AD continuum. Research has focused mainly on menopause and MHT, while several other female reproductive factors remain understudied. Evidence is especially limited for blood- and CSF biomarkers, and longitudinal biomarker change. Variation in exposure definitions, hormone assays, treatment formulations, APOE genotype, age, and clinical stage further limits comparison across studies.

To our knowledge, no previous systematic review has comprehensively synthesized this evidence across core AD pathology. Such a review is needed to determine whether reproductive and hormonal factors are associated with specific biological processes underlying AD and to identify priorities for future research.

Accordingly, this systematic review aims to (1) evaluate associations between female- and male-specific reproductive and hormonal factors and AD-related biomarkers (2) identify which reproductive and hormonal factors (e.g., age of menarche, parity, reproductive disorder, endogenous hormone levels, hormonal contraceptives, MHT) show consistent associations with AD-related biomarkers, and (3) evaluate whether these associations differ across biomarkers of amyloid, tau, neurodegeneration or neuronal injury, cerebral metabolism, and cerebrovascular or white-matter integrity.

Methods

Search strategy and selection criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline⁵⁵ and prospectively registered in the international Prospective Register of Systematic Review (PROSPERO; registration number CRD420261363648).

We searched three electronic databases: MEDLINE (Ovid), Embase and Web of Science (Clarivate Analytics). The search strategy was developed in MEDLINE in collaboration with librarians at Karolinska Institutet (Stockholm, Sweden). For each search concept, Medical Subject Headings (MeSH-terms) and relevant free-text terms were identified. The search strategy was subsequently translated into other databases, partly using Polyglot Search Translator.⁵⁶ The full search strategy is available in appendix **pp 3-15**.

The review was restricted to studies published in English to ensure that all reviewers could independently read, critically appraise and extract data from eligible studies. Databases were searched from inception through 11 April 2025 and updated on 26 February 2026. Reference lists and forward citations of included studies were screened for additional records. All retrieved records were imported into Covidence,⁵⁷ de-duplicated, and screened independently by two reviewers (MSN and YW) based on titles and abstracts. Full-text articles deemed potentially eligible were subsequently assessed independently by two reviewers (MSN and EK) against the predefined eligibility criteria. Disagreements between reviewers were resolved through discussion and, when necessary, consultation with three senior authors (S Mitra, S Maioli and SS) until consensus was reached. A list of studies excluded at full-text screening stage is provided in the **appendix pp 16-18**.

Search terms for male- and female-specific reproductive and hormonal factors were primarily adapted from Han and colleagues,⁵⁸ and supplemented with additional terms identified by the review team. The exposure search strategy encompassed menstrual and reproductive factors, parity, fertility-related factors, pregnancy disorders, gynecological conditions and surgeries, endogenous and exogenous hormonal exposures, hormonal therapies, and reproductive endocrine disorders. Outcome search terms captured AD-related biomarkers across the A/T/N framework,⁵⁹ including biomarkers of amyloid pathology (A), tau pathology (T), and neurodegeneration (N), assessed using blood, CSF, PET, MRI, diffusion tensor imaging (DTI), and FDG-PET. Although the 2024 NIA-AA criteria⁶⁰ expanded this framework by distinguishing early secreted phosphorylated tau (T1) from later tau proteinopathy (T2) and incorporating additional domains, including inflammation (I), α -synuclein (S), and vascular injury (V), these classifications have not yet been widely adopted in observational studies, including those investigating sex-specific reproductive and hormonal exposure. Therefore, outcomes were organized according to the A/T/N framework.

Owing to the limited availability of randomized controlled trial (RCT) evidence and the wide range of reproductive and hormonal factors examined in the literature, both randomized and observational study designs were included to ensure a comprehensive evaluation of the evidence base. To be included in the review, studies had to include middle-aged and older adults (aged ≥ 40 years or with a mean age ≥ 40 years), either community-dwelling individuals or individuals with MCI, dementia, or AD. Eligible studies were required to examine at least one reproductive or hormonal exposure of interest in relation to at least one AD-related biomarker outcome within the A/T/N framework and to clearly address a research question aligned with the objectives of this review.

The exclusion criteria were as follows: (1) non-human studies, including preclinical and animal studies; (2) postmortem studies; (3) studies of early onset or familial AD or dementia; (4) studies including participants with neurodegenerative disorders other than AD (e.g., Parkinson's disease); (5) studies in which participant selection was based on medical conditions unrelated to reproductive or hormonal exposures of interest (e.g., cancer status or BRCA mutation carriers); (6) studies of hormone therapy prescribed for non-menopausal indications; (7) studies primarily investigating omics-based biomarkers;

and (8) studies involving transgender hormone use or gender-affirming surgery. Gray literature and conference abstracts were excluded.

Although earlier studies used terms such as hormone replacement therapy (HRT), hormone therapy (HT), or estrogen replacement therapy (ERT), MHT is now the preferred term according to leading organizations, including the Australasian Menopause Society and the North American Menopause Society. While some studies may have used these therapies for indications other than menopausal symptom management, given the scope of this review they are assumed to relate primarily to menopause care; therefore, HRT, HT, and ERT are hereafter collectively referred to as MHT.

Data extraction

Data from each included study was extracted using a piloted, standardized Excel spreadsheet. One reviewer (MSN) extracted data, which was subsequently validated by a second reviewer (EK). Extracted information included study characteristics (study design, recruitment methods, inclusion and exclusion criteria), sample characteristics (sample size, age, sex, race or ethnicity, cognitive status and/or cognitive test scores, and apolipoprotein ε4 [APOE] carrier status), exposure and outcome measures and their ascertainment, statistical analyses (including analytical approach, and covariates used for adjustment), main findings, and study limitations. Study authors were not contacted for clarification or to obtain additional information when relevant data was unclear or unavailable in the study publication.

Risk-of-bias assessment of included primary studies

Risk of bias and study quality were assessed using study design-specific appraisal tools. . The Cochrane Risk of Bias 2 (RoB-2) tool was used to evaluate RCTs. Cohort and case-control studies were evaluated using the design-specific versions of the Newcastle-Ottawa Scale (NOS), while cross-sectional studies were evaluated using the adapted NOS for cross-sectional studies (NOS-xs).⁶¹ Assessment were completed by one reviewer (MSN) and independently validated by a second reviewer (EK or PP), with disagreements resolved through discussion and consensus with senior authors. Risk of bias is summarized in the **appendix (pp 19-23)**.

Data synthesis

Studies were first grouped according to outcome domain (amyloid pathology, tau pathology, and neurodegeneration). Neurodegeneration outcomes were further classified into commonly reported measures, including cerebral glucose metabolism, white matter hyperintensities, hippocampal volume, and gray and white matter volumes, with less frequently reported neuroimaging outcomes summarized separately. Studies were then organized according to broad exposure categories, including menstrual, reproductive, and parity-related factors; gynecological conditions, reproductive surgeries, and pregnancy disorders; menopausal status; hormonal therapies; exogenous hormones and endogenous hormones and gonadotropins. A narrative synthesis was undertaken, supported by use of tabulation of study characteristics and vote counting based on the direction of effect.

Results

A total of 35,331 records were identified across three databases (Fig. 1), following which 9,715 duplicates were removed before screening and 3 additional records from reference searches were added. In total, 25,619 records were screened. Full-text assessment was conducted for 180 articles, of which 101 met the inclusion criteria and were included in the review. Several studies examined multiple sex-specific reproductive and hormonal factors in relation to various outcomes. Detailed study characteristics, methods and materials, and findings for all included studies have been extracted and are provided in the **appendix (pp 24–167)**. MRI specifications for included imaging studies are summarized in the **appendix (pp 168–173)**.

Risk-of-bias assessment

Among the cross-sectional studies, 39% (n = 33) were rated as having a low risk of bias, 57% (n = 48) as moderate risk, and 4% (n = 3) as high risk. Of the 15 cohort studies, 13% (n = 2) were judged to be at low risk of bias, while the remaining 87% (n = 13) were rated as moderate risk; none were classified as high risk (**eFigure 1, appendix pp 178**). Three case-control studies were included: one rated as high risk, whereas the other two were judged to be at moderate risk. Among the 12 RCTs, eight were judged to have some concerns regarding risk of bias, while four were rated as having a high risk of bias (**eFigure 2, appendix pp 178**).

Tau pathology

Nineteen studies investigating tau outcomes were included.^{11,20,29–33,36,37,40,54,62–69} The majority of studies used a cross-sectional design (n = 13),^{11,29,30,33,36,37,40,54,62,64–66,68} followed by longitudinal (n = 5)^{31,32,54,63,67} and RCTs (n = 2).^{20,69} One study contributed both cross-sectional and longitudinal data through separate cohorts; therefore, study design counts exceed the number of included studies. Studies were primarily conducted in the United States (n = 14), followed by Canada (n = 3);^{37,54,64} Belgium,³² China,⁵⁴ Germany,⁶⁸ Singapore,⁴⁰ Sweden,³⁶ and Switzerland⁶⁶ each contributed one study. When exposures were counted across all relevant categories, MHT was the most frequently investigated exposure (n = 10),^{20,30–33,62–64,66,69} followed by reproductive factors (n = 5),^{29,30,36,63,66} endogenous hormones and gonadotropins (n = 3),^{37,54,67} and menopausal status (n = 2).^{29,68} Reproductive surgery,¹¹ pregnancy disorders,⁴⁰ and vasomotor symptoms⁶⁵ were each examined in one study.

Data overlap across studies was common, with several studies drawing from the same cohort or family of studies: three studies used data from Alzheimer's Disease Neuroimaging Initiative (ADNI),^{37,54,64} two from the Framingham Health Study (FHS),^{29,67} two from the Wisconsin Registry for Alzheimer's Prevention (WRAP),^{30,33} and two studies were derived from the Rochester Epidemiology Project (REP) medical records–linkage system.^{11,63} Across the studies, participants were generally older adults, with

age ranging from 42.5 to 75 years. Total analytical sample size varied considerably, from 52 to 2,784 participants.

Exogenous hormone exposure

Among the five cross-sectional studies,^{30,33,62,64,66} three found no association between MHT use^{30,33,66} and tau biomarkers. One observed trend-level evidence of lower regional tau-PET burden among women with a history of MHT use,⁶² while another reported lower tau-PET burden, and lower CSF and lower plasma p-tau181 levels among MHT users compared with non-users.⁶⁴ Although no overall association between MHT use and regional tau-PET burden was observed,³⁰ women who initiated MHT more than five years after menopause had higher regional tau-PET burden. In addition, MHT use was associated with greater tau burden only in the presence of elevated amyloid levels.³⁰

One longitudinal study of community-dwelling older women found no association between ever use of hormonal contraception and temporal tau-PET burden over repeated imaging assessments.⁶³

Longitudinally, two studies reported no association between MHT use and changes in tau biomarkers.^{32,63} In a longitudinal study of healthy MHT-naïve postmenopausal women (mean age 54 years), who either initiated MHT (N = 193) or opted to remain untreated (N = 31) and were followed for approximately 6 months, no association was observed between MHT use and changes in plasma p-tau231 or total tau levels.³² Similarly, a longitudinal study of community-dwelling older women (median age 71 years) with repeated imaging assessments over 8 years of follow-up found no association between MHT use and temporal tau-PET burden.¹⁵ In contrast, another longitudinal study reported no overall association between MHT use and tau accumulation; however, MHT use was associated with tau accumulation in an age-dependent manner.³¹ Older women (> 70 years of age) with a history of MHT use (N = 73), exhibited faster regional tau accumulation than age-matched non-users (N = 73) in the period of over 3.5 (SD 1.5) years, whereas little to no association was observed among younger women. Increased tau accumulation was observed in the entorhinal cortex, inferior temporal gyrus, and temporal fusiform gyrus.

In the Women's Health Initiative Memory Study (WHIMS) randomized controlled trial, the rates of change in plasma p-tau217 and p-tau181 measured at two time points over a mean follow-up of approximately 15 years did not differ significantly between women randomized to estrogen alone (N = 575), estrogen plus progestin (N = 829), or placebo (N = 577 or N = 803 respectively).⁶⁹

Overall, findings regarding MHT and tau pathology were inconsistent. While some cross-sectional studies reported lower tau burden among MHT users and others found higher tau burden under specific conditions, such as elevated amyloid burden or late MHT initiation, most longitudinal and randomized trial evidence did not support a clear association between MHT use and tau biomarkers.

Endogenous hormones and gonadotropins

Cross-sectionally, one study reported that lower testosterone levels were associated with higher CSF p-tau181 concentrations in both older men and women,³⁷ whereas a time-lagged study found no association between midlife testosterone levels and tau-PET burden measured approximately 15 years later in either sex.⁶⁷ Findings for sex hormone-binding globulin (SHBG) were inconsistent. One study reported no association between plasma SHBG levels and CSF p-tau181 concentrations (N = 707),⁵⁴ whereas a time-lagged study found that higher midlife SHBG levels were associated with lower regional tau-PET burden in the entorhinal, inferior temporal, and rostral middle frontal cortices at late-life follow-up among men alone (N = 159).⁶⁷ No associations between plasma estradiol levels and tau-PET burden were observed among women in the time-lagged study.⁶⁷ Overall, evidence for associations between endogenous hormones and gonadotropins was limited and inconsistent.

Reproductive and parity-related factors

Five studies examined age at menopause in relation to tau pathology,^{29,30,36,63,66} with inconsistent findings. Cross-sectionally, three studies found no association between age at menopause and tau-PET burden,^{30,36,66} while another reported higher tau-PET burden in the rostral middle frontal and lateral occipital regions among women reporting menopause before age 50 years compared with those reporting later menopause; however, these associations did not remain significant after multiple testing correction.²⁹ In contrast, a longitudinal study of community dwelling older women with repeated imaging follow-up of up to 8 years found that younger age at menopause was associated with lower temporal tau-PET burden.⁶³ One study further reported that earlier age at menopause was associated with higher regional tau-PET burden only in the presence of elevated amyloid burden among cognitively unimpaired older women with parental history of AD.³⁰ Overall, findings were inconsistent, with a trend-level and an amyloid-dependent cross-sectional association suggesting greater tau burden with earlier menopause, whereas the only longitudinal study reported a small association in the opposite direction.

Two studies examined age at menarche and reproductive period/window in relation to tau pathology.^{36,63} Earlier age at menarche and a longer reproductive period was associated with higher CSF p-tau levels in one cross-sectional study,³⁶ whereas a longitudinal study found no association between age at menarche or reproductive window and temporal tau-PET burden.⁶³ Overall, findings for reproductive factors were limited and inconsistent, with associations varying according to the reproductive exposure assessed, study design, and tau biomarker used.

Menopause status

Two cross-sectional studies examined self-reported menopausal status in relation to tau pathology, and neither reported a significant association with tau-PET burden²⁹ nor with plasma p-tau181 levels.⁶⁸

Other female-specific factors

One cross-sectional study examined vasomotor symptoms in relation to tau pathology but found no association between either objectively measured or self-reported vasomotor symptoms and plasma p-tau181 or p-tau231 levels.⁶⁵ One cross-sectional study reported that a history of pregnancy hypertension was associated with higher serum p-tau217 levels among community-dwelling midlife women (N = 68), independent of age, cognitive status, vascular risk factors, renal function, and APOE ε4 carrier status.⁴⁰ One cross-sectional study examined premenopausal bilateral oophorectomy (PBO) in relation to tau pathology and found no independent association between either early (< 46 years, N = 61) or late (46–49 years, N = 51) PBO and tau-PET burden.¹¹ However, women who underwent early PBO exhibited higher tau-PET burden in the presence of elevated amyloid levels as compared to age-matched referent women who did not undergo PBO, whereas no such association was observed among women with late PBO.¹¹

Amyloid pathology

Twenty-eight studies examined amyloid outcomes.^{11,14,20,21,25,28,29,31–36,38,39,44,49,53,54,62–65,67,69–72} The majority of them used a cross-sectional design (n = 18),^{11,14,25,29,33,34,36,38,39,44,49,53,54,62,64,65,70,72} followed by longitudinal studies (n = 6)^{31,32,35,54,63,67} RCTs (n = 4),^{20,21,28,69} and case-control design (n = 1).⁷¹ One study contributed both cross-sectional and longitudinal data;⁵⁴ therefore, study design counts exceed the number of included studies. Studies were primarily conducted in the United States (n = 21),^{11,14,20,21,25,28,29,31,33,35,44,54,62–65,67,69,71,72} followed by Australia (n = 3),^{38,49,53} South Korea (n = 3)^{34,39,70} and Canada (n = 2).^{54,64} Belgium,³² China⁵⁴ and Sweden³⁶ contributed one study each. When exposures were counted across all relevant categories, MHT was the most frequently investigated exposure (n = 12),^{14,20,21,28,30–33,62–64,69} followed by endogenous hormones and gonadotropins (n = 8).^{34,38,39,49,53,54,67,72} Three studies examined reproductive and parity-related factors,^{36,63,70} five examined menopause status,^{14,25,29,35,44} three examined gynecological conditions and reproductive surgery studies,^{11,14,71} and one examined vasomotor symptoms.⁶⁵

Several studies were based on overlapping cohorts. Three studies were derived from the REP medical records–linkage system,^{11,63,71} while two studies each used data from the FHS,^{29,67} ADNI,^{54,64} and Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer’s Disease.^{34,70} The total analytical sample size ranged from 18 to 2,784 participants. Study populations were predominantly composed of older adults, with most cohorts having a mean or median age of 60 years or older. Across studies, participant age ranged from approximately 40 to 82 years.

Exogenous hormone exposure

Of the four cross-sectional studies,^{14,33,62,64} three reported no overall association between MHT use and amyloid biomarkers, including global amyloid PET burden,^{62,64} and CSF amyloid biomarkers.³³ One study found MHT use associated with higher orbitofrontal gyrus Pittsburgh compound-B (PiB) uptake among community-dwelling cognitively unimpaired middle-aged women.¹⁴ Although overall associations between MHT use and amyloid biomarkers were largely null across cross-sectional studies, APOE ε4

status appeared to modify these associations in some populations.^{33,64} In a study among cognitively unimpaired older women at higher AD risk, APOE ϵ 4 carriers who used MHT had higher CSF p-tau/A β 42 ratio and lower CSF A β 42/40 ratios than non-users and non-carriers, both users and non-users.³³ Whereas another study among postmenopausal women across the AD spectrum suggested that MHT may attenuate APOE ϵ 4-associated amyloid pathology, as APOE ϵ 4-related differences in amyloid burden were observed among non-users but not among MHT users.⁶⁴ Overall, the available cross-sectional evidence suggests that APOE ϵ 4 may modify the relationship between MHT and amyloid pathology; however, findings are inconsistent and may partly reflect differences in the underlying study populations and disease risk profiles.

One longitudinal study of community-dwelling older women (N = 389) found no association between ever use of hormonal contraception and global amyloid-PET burden over repeated imaging assessments.⁶³

None of the three longitudinal studies found an association between MHT use and changes in plasma amyloid biomarkers,³² or global amyloid PET burden,^{31,63} with follow-up durations ranging from around 6 months³² to 8 years.⁶³ However, among healthy, recently menopausal women, APOE ϵ 4 status appeared to modify longitudinal biomarker trajectories, with MHT users carrying at least one APOE ϵ 4 allele showing a smaller reduction in the A β 42/p-tau231 ratio over approximately 6 months than APOE ϵ 4 carrier non-users, suggesting a more favorable amyloid-related biomarker trajectory.³²

Four studies were based on RCTs.^{20,21,28,69} Among postmenopausal women with AD, short-term transdermal estradiol reduced plasma A β 40 concentrations among HRT-naïve women, although the effect was transient and not sustained after treatment cessation.²⁸ Among healthy recently postmenopausal women with good cardiovascular health from the Kronos Early Estrogen Prevention Study (KEEPS) trial (median age 60 years), transdermal 17 β -estradiol (tE2) was associated with lower cerebral amyloid deposition than placebo, particularly among APOE ϵ 4 carriers, whereas oral conjugated equine estrogen (oCEE) was not associated with cerebral amyloid deposition.²¹ These findings were observed approximately 3 years after completion of the 4-year treatment period.²¹ In contrast, long-term follow-up of the KEEPS cohort (≈10 years after trial completion; mean age 68 years), neither oCEE nor tE2 exposure was associated with brain A β burden compared with placebo, and APOE ϵ 4 carrier status did not modify these findings.²⁰ Similarly, the WHIMS trial found no association between randomization to MHT and 15-year changes in plasma A β 42/A β 40 ratios.⁶⁹ Overall, evidence from RCTs was mixed, with some evidence supporting a short-term or intermediate-term beneficial effect of transdermal estradiol on amyloid biomarkers, whereas longer-term follow-up studies generally reported no association.

Endogenous hormones and gonadotropins

Seven studies cross-sectionally^{38,39,49,53,54,63,72} and two studies longitudinally^{54,67} examined circulating sex hormones, gonadotropins, and SHBG in relation to amyloid pathology.

Evidence for luteinizing hormone (LH) was mixed. Higher serum LH levels were associated with increased plasma A β 40 levels, independent of age, body mass index, cognition and other hormones, among cognitively normal older men from Australia (n = 40).³⁸ However, LH was not associated with plasma A β 40 levels in another small study of older men from a memory clinic (n = 28).⁴⁹ Among men across the AD spectrum, elevated LH levels were associated with increased plasma A β levels and greater brain amyloid burden in those with subjective memory complaints, but not among individuals with MCI or AD, suggesting that LH-related associations may be most evident at preclinical stages.⁵³ In a mixed community- and memory clinic-based sample of older adults from South Korea, LH was not associated with cerebral A β positivity in men, although higher LH levels were associated with greater cerebral A β positivity among postmenopausal women.³⁴ In contrast, among midlife women at increased risk of AD, LH was not independently associated with regional PET amyloid burden after multivariable adjustment.⁷² Overall, findings for LH were mixed, with no clear or consistent association with amyloid pathology across populations, sexes, or disease stages.

Evidence for Follicle-stimulating hormone (FSH) was more consistent. In a mixed community- and memory clinic-based cohort of older adults from South Korea, higher FSH levels were associated with greater cerebral A β positivity among women, whereas no association was observed in men.³⁴ Among cognitively normal midlife women at increased risk of AD, higher FSH levels were associated with greater regional PET amyloid burden, particularly in frontal regions, with associations most pronounced in postmenopausal women.⁷² Consistent with these findings, in postmenopausal women aged ≥ 60 years across the AD spectrum, FSH levels were highest in women with AD dementia, followed by those with MCI and cognitively normal women. Higher FSH levels were associated with increased odds of amyloid positivity and greater global and regional amyloid burden independent of APOE ϵ 4 status.³⁹ Overall, higher FSH levels were consistently associated with less favorable amyloid biomarker profiles in women.

Evidence for SHBG was relatively consistent across studies. In a memory clinic sample of older men from Australia, higher SHBG levels were associated with higher plasma A β 40 concentrations independent of age.⁴⁹ In non-demented older adults from China, higher plasma SHBG levels were associated with lower CSF A β 42 concentrations cross-sectionally, and with a faster decline in CSF A β 42 over time, both suggestive of greater amyloid pathology.⁵⁴ In contrast, a longitudinal study from community-dwelling adults found no association between midlife SHBG levels and later-life global amyloid burden measured using PET in neither men nor women.⁶⁷

Evidence for testosterone was inconsistent. In a memory clinic sample of older men from Australia, lower total and free testosterone levels were associated with higher plasma A β 40 concentrations.⁴⁹ Similarly, among men across the AD spectrum, lower calculated free testosterone levels were associated with greater brain amyloid burden in individuals with MCI, although no association was observed in those with subjective memory complaints or AD.⁵³ In contrast, free testosterone was not associated with plasma A β 40 levels in cognitively normal older men.³⁸ In a mixed community- and memory clinic-based

cohort from South Korea, higher free testosterone levels were associated with greater cerebral A β positivity among postmenopausal women, whereas no association was observed in men.³⁴

Evidence for estradiol was largely null. In older men from Australia, estradiol was not associated with plasma A β 40 levels.⁴⁹ Similarly, in a mixed community- and memory clinic–based cohort of older adults from South Korea, neither total nor free estradiol levels were associated with cerebral A β positivity among postmenopausal women.³⁴ Among postmenopausal women aged ≥ 60 years across the AD spectrum, estradiol levels were not associated with amyloid positivity or global or regional amyloid burden.³⁹ Likewise, a longitudinal study found no association between midlife estradiol levels and later-life global amyloid PET burden measured approximately 15 years later.⁶⁷ Overall, available evidence consistently found no association between estradiol levels and amyloid pathology.

Menopause status

Five studies examined menopausal status in relation to amyloid pathology.^{14,25,29,35,44} Four studies from closely related cohorts of cognitively unimpaired middle-aged women examined menopausal status in relation to amyloid pathology, including three cross-sectional studies^{14,25,44} and one longitudinal study.³⁵ In a cross-sectional study of cognitively normal midlife women ($n = 42$), menopausal stage was classified using the Stages of Reproductive Aging Workshop (STRAW) criteria, clinical judgement, and menopausal symptoms. Perimenopausal and postmenopausal women exhibited greater regional PiB uptake than premenopausal women, with a progressive increase in amyloid burden across menopausal stages (premenopausal < perimenopausal < postmenopausal).⁴⁴ Amyloid burden was greatest among APOE ϵ 4-positive postmenopausal women, and women exhibited greater PiB uptake than age-matched men ($n = 18$).

Similarly, in a larger cross-sectional study of cognitively intact women aged 40–65 years ($n = 161$), menopausal stage was classified using STRAW criteria and corroborated with hormone assessments. Although no significant differences in amyloid burden were observed across menopausal stages after adjustment for age and cerebellar uptake, postmenopausal women showed higher PiB uptake than premenopausal women after additional adjustment for APOE ϵ 4 status, with similar trends observed for perimenopausal women.²⁵

Findings were further supported by another cross-sectional study from a similar cohort ($n = 121$; mean age 53 [SD 7] years), which identified menopausal status as the predictor most consistently associated with higher regional PiB uptake across all regions examined.¹⁴ In the only longitudinal study with similar status assessment as Mosconi 2018,³⁵ perimenopausal ($N = 14$) and postmenopausal women ($N = 12$) exhibited greater amyloid accumulation over 3 years than premenopausal women ($N = 15$), with increases in frontal PiB uptake observed in both groups and additional increases in posterior cingulate amyloid burden among postmenopausal women.³⁵

In contrast, a larger cross-sectional study from the FHS (n = 161, mean age = 57 [10] years) found no association between menopausal status and global A β -PET burden.²⁹

Reproductive and parity-related factors

Two studies examined age at menopause, age at menarche, and reproductive window/period in relation to amyloid pathology.^{36,63} In a population-based sample of women free from dementia and with natural menopause followed over 25 years (N = 75), age at menopause was not associated with CSF A β biomarkers, whereas earlier age at menarche was associated with a lower CSF A β 42/A β 40 ratio and a longer reproductive period was associated with lower A β 42 levels and a lower CSF A β 42/A β 40 ratio.³⁶ In contrast, a longitudinal study of community-dwelling women (N = 389) found no association between age at menarche, age at menopause, or reproductive window and changes in global amyloid PET burden.⁶³

Two studies examined parity in relation to amyloid pathology.^{63,70} In a cross-sectional study of older women with normal cognition (N = 148) or MCI (N = 89), grand parity (≥ 5 births) was not associated with either global A β deposition or A β positivity compared to 0–4 births.⁷⁰ In contrast, a longitudinal study of older women with repeated imaging assessments over around 6–8 years found that having five or more pregnancies lasting > 20 weeks (N = 59) was associated with greater amyloid PET accumulation, independent of age, education, APOE and cardiovascular risk factors and conditions for or possible mediators.⁶³ Nevertheless, the authors acknowledge that the absence of a dose-response relationship between a greater number of pregnancies and any imaging outcome may in their study may indicate that the finding arose by chance, particularly in light of the exploratory nature of the analyses and the lack of correction for multiple testing.⁶³

Gynecological conditions and reproductive surgery

In a cross-sectional study of cognitively unimpaired middle-aged women (mean age 53 [SD 6] year), self-reported hysterectomy status was associated with higher PiB β -amyloid deposition in the superior frontal gyrus, medial frontal gyrus, and anterior cingulate cortex.¹⁴ In contrast, a nested case-control study of women who underwent bilateral salpingo-oophorectomy (BSO) before age 50 years and before reaching natural menopause, regardless of concurrent or prior hysterectomy (n = 23; median age 65 years), reported higher cortical PiB uptake than age-matched controls (n = 20; median age 63 years), although the difference was not statistically significant.⁷¹ Similarly, in a related population identified through the same record-linkage system, a cross-sectional study found no significant association between PBO before age 50 years and overall PET amyloid burden among women aged ≥ 60 years, regardless of whether PBO occurred before age 46 years (n = 61) or between ages 46 and 49 years (n = 51), compared to age-matched controls (n = 108).¹¹

Vasomotor symptoms

Among late perimenopausal and postmenopausal women (N = 274) without a history of hysterectomy, bilateral oophorectomy, or MHT use, greater objectively measured nighttime vasomotor symptoms were associated with a lower plasma A β 42/A β 40 ratio.⁶⁵ No associations were observed for 24-hour or wake-time vasomotor symptoms, or for subjectively reported vasomotor symptoms.

Cerebral glucose metabolism (FDG-PET)

Nine studies investigated cerebral glucose metabolism using FDG-PET^{14,25,35,43–46,54,73} including regional or whole-brain-normalized measures of glucose metabolism. Five were cross-sectional^{14,25,43,44,73} and four were longitudinal^{35,45,46,54} with follow-up durations ranging from approximately two to three years. The most common exposure studied was menopausal status, followed by MHT or estrogen use, CSF estradiol concentrations, plasma SHBG, and hysterectomy status. Most studies were conducted in the USA^{14,25,35,43–46}, with one from Germany⁷³ and one⁵⁴ from both USA and Canada. Most studies used relative or reference-normalized FDG measures rather than absolute kinetic cerebral metabolic rate of glucose (CMR_{glc}).

Exogenous hormone exposures

Three American studies^{14,45,46} examined estrogen or MHT use in relation to FDG-PET metabolism. Rahman et al.¹⁴ reported that MHT use was associated with higher FDG uptake, particularly in frontal and parietal regions. In sensitivity analyses, postmenopausal MHT users showed higher metabolism than postmenopausal non-users.

Rasgon et al.⁴⁶ was a small longitudinal pilot study that included 12 postmenopausal. Over approximately two years, estrogen users showed increased lateral temporal glucose metabolism, whereas non-users showed no significant metabolic change in this region. Rasgon and colleagues⁴⁵ extended this work in 20 postmenopausal women (estrogen users = 11, non-users = 9). Over two years, estrogen non-users showed significant posterior cingulate metabolic decline, while estrogen users showed no significant decline in this region. Both these studies were observational and ascertained estrogen exposure through reproductive or medication histories, without documented external validation.

Endogenous hormone exposures

One small cross-sectional study examined endogenous estradiol concentrations.⁷³ In six postmenopausal women with probable AD, CSF estradiol concentrations were positively correlated with glucose metabolism in the left hippocampus, suggesting that higher endogenous estrogen levels were associated with greater regional brain metabolism.

Xu and colleagues⁵⁴ investigated plasma SHBG as a predictor of longitudinal neurodegeneration in 448 cognitively normal or mildly cognitively impaired men and women on average 75 years old from ADNI. Over approximately five years of follow-up, higher baseline plasma SHBG concentrations predicted faster

decline in brain glucose metabolism, independent of age, sex, education, APOE ε4 status, and baseline clinical diagnosis (cognitively normal or MCI).

Menopausal status

Five studies assessed menopausal status in relation to CMRglc.^{14,25,35,43,44} All originated from the same community-based cohort in the USA of cognitively normal middle-aged women (approximately 40–65 years), classified as premenopausal, perimenopausal, or postmenopausal using STRAW10+ -based criteria. These studies differed slightly in sample size and research questions. Across the cross-sectional studies, later menopausal stage was generally associated with lower glucose metabolism in AD-vulnerable regions, particularly the posterior cingulate/precuneus, frontal, temporal, and parietal cortices. One of the studies by Mosconi et al.³⁵ extended these findings longitudinally, reporting greater metabolic decline over approximately 2–3.5 years among peri- and postmenopausal women than among premenopausal women. Rahman et al.¹⁴ further found that menopausal status was one of the strongest predictors of lower FDG metabolism when considered alongside demographic, vascular, hormonal, and lifestyle risk factors.

Other female-related factors

Hysterectomy was examined in the study by Rahman et al.¹⁴ It was not retained as an independent predictor of FDG metabolism in the primary multivariable models. However, sensitivity analyses suggested a trend toward lower FDG uptake among women with previous hysterectomy compared with those without hysterectomy.

Neurofilament light (NfL)

There were four studies that reported NfL as an outcome - a longitudinal,³² cross-sectional,⁶⁵ nested case-control,⁶⁸ and an RCT,⁶⁹ spanning across Belgium, USA (MsBrain study cohort; WHIMS cohort) and Germany (ESTHER study cohort). Exposures related were women receiving MHT (longitudinal³², Belgium), vasomotor symptoms (cross-sectional⁶⁵ MSBrain study, USA), menopause status (nested case-control, ESTHER, Germany), and in the RCT examined assigned HT⁶⁹ (USA, WHIMS). NfL was measured in the blood plasma in all studies and analyzed using the single molecule array Simoa.

Exogenous hormone exposures

When examining MHT and NfL in the longitudinal study there was no difference between the MHT users vs controls at baseline or over the 6-month follow-up.³² However, treatment allocation was not randomized; rather, women self-selected whether to receive treatment, increasing the risk of confounding. In addition, the follow-up period was relative short (approximately six months).³²

In the RCT⁶⁹ using the WHIMS cohort of cognitively unimpaired postmenopausal women, no differences were observed in the increase in NfL over time between participants receiving estrogen alone or estrogen plus progestin and those receiving placebo.

Menopause status

In a nested case-control study matched on dementia status, investigating menopause status and NfL, there was no association even after controlling for age and APOE e4 status.⁶⁸ However, the ascertainment of menopause status was not confirmed with hormone levels thus there is a risk of misclassification.

Other female-related factors (dup: abstract ?)

In the cross-sectional study⁶⁵ from the MsBrain cohort, including 248 community-recruited, nondemented women who were perimenopausal or postmenopausal, in the adjusted models, neither objective nor self-reported vasomotor symptoms were associated with NfL.

White matter hyperintensities, cerebral small vessel disease, and white matter integrity

There were 26 cross-sectional studies,^{25–27,70,74–95} five longitudinal cohorts,^{12,51,63,96,97} two case–control studies,^{71,98} and six RCTs.^{18,22,99–102} With most of studies concentrated in USA and the UK. Several reports were derived from overlapping cohorts, particularly UK Biobank, WHIMS, and KEEPS. Where ethnicity was reported, many cohorts were predominantly White; however, studies from China, Japan, South Korea, and several more racially and ethnically diverse US pregnancy cohorts were also represented.

Outcomes primarily comprised WMH or lesion volume, with some studies also assessing infarcts, lacunes, microbleeds, perivascular spaces, and diffusion-based measures of WM integrity. Outcome assessment methods varied across studies ranging from visual rating scales, such as the Fazekas Scale and the Cardiovascular Health Study scale, to semi-automated and fully automated volumetric segmentation techniques, contributing to methodological heterogeneity.

Exogenous hormone exposures

Most observational studies found no association between MHT and white matter lesion (WML) burden, infarcts, or lesion progression.^{63,76,81,83,87,97} Similarly, WHIMS trial analyses found no effect of CEE, with or without medroxyprogesterone acetate (MPA), on ischemic lesion volume or progression.^{18,99} In the KEEPS trial, neither oral nor transdermal estrogen affected WMH progression over 48 months,¹⁰¹ although greater progression with oral CEE was reported at 84 months.²² No long-term differences were evident approximately 14 years after randomization.¹⁰⁰ Some observational findings suggested greater lesion burden with later initiation or longer use, but these associations were inconsistent.^{63,95,100} Evidence for hormonal contraception was limited, with a single study reporting better WM integrity and lower lesion volume among previous users.⁶³

Endogenous hormone exposures

Findings varied by hormone. In women, higher estrone and testosterone were associated with lower WMH volume, whereas higher FSH was associated with greater lesion burden in some studies.^{26,79} Estradiol was generally not independently associated with WMHs. Studies in men were predominantly null^{51,89} although one study linked higher bioavailable estradiol with lacunes.⁷⁷ Greater cumulative endogenous hormone exposure was associated with lower lesion volume in one large cohort.⁷⁵

Menopause status

Some studies found greater WMH burden among postmenopausal women or women with earlier menopause,^{12,81,86,90} or lower WM-fractional anisotropy (FA) among postmenopausal compared to perimenopausal, but not premenopausal.²⁵ However, age-matched analyses and other longitudinal studies found no association with menopausal status, age at menopause, or reproductive-window length.^{27,63} Findings for age at menarche were inconsistent.^{63,88}

Reproductive and parity-related factors

Hypertensive disorders of pregnancy were associated with greater regional WMH burden or poorer diffusion-based WM integrity in some studies,^{78,96} although other studies found no significant difference in total lesion volume.^{85,96} Associations with parity and gravidity were inconsistent, ranging from no association to higher lesion, lacune, or microbleed prevalence with more pregnancies or deliveries.^{70,74,88,94}

Other female-related factors

More objectively measured hot flashes, particularly during sleep, were associated with greater total, deep, periventricular, and frontal WMH burden.^{91,92} Self-reported vasomotor symptoms were not associated with imaging outcomes.

One matched case–control study found that polycystic ovary syndrome (PCOS) was associated with more deep WMLs and lacunar infarcts,⁹⁸ while a cross-sectional study found no association between PCOS and abnormal WM, but an association with lower total WM-FA.⁹³ PBO, particularly before age 40, was associated with poorer diffusion-based WM integrity⁸⁴ but not consistently with greater WMH volume or infarcts.^{71,84}

Total brain, global gray-matter, and global white-matter volumes

There were 23 studies that reported total brain, global gray matter, or WM volumes as outcomes, ranging in sample sizes from 35 to 11,604 participants. There were 15 cross-sectional studies,^{9,13,14,24,74,76,82,86,87,90,93,103–106} three cohort studies,^{12,51,107} and five RCTs.^{18,22,23,99,101} Studies were conducted primarily in the United States and United Kingdom, with additional cohorts from the Netherlands, South Korea, Australia, and France.

Exogenous hormone exposure

Nine cross-sectional studies^{9,13,14,24,76,82,87,90,104} reported on associations between exogenous hormone exposures and total brain gray matter, and WM volume, and five RCTs,^{18,22,23,99,101} but no cohort studies.

In WHIMS-MRI, women previously assigned to CEE-based therapy had slightly lower total brain volume than placebo-treated women,²³ although over a mean 4.7 years between the two scans, prior therapy did not accelerate annual total brain volume loss.¹⁸ In a conditional analysis from the same cohort, smaller total brain volume accompanied the development of cognitive impairment among CEE-assigned but not placebo-assigned women; this was not an overall treatment effect.⁹⁹

In KEEPS, neither oral CEE nor transdermal estradiol altered whole-brain volume change relative to placebo at four years¹⁰¹ or seven years.²²

Greater global gray matter volume (GMV) in female hormone therapy users was reported in two cross-sectional studies,^{9,104} whereas smaller GMV in current users was reported by Greenberg et al.⁷⁶ and by Ryan et al.⁸⁷. Postmenopausal MHT use was associated with lower total cerebral brain volume in the Framingham Offspring cohort, among women aged ≥ 60 years.¹³ Four cross-sectional studies reported null results, with three reporting a nonsignificant trend favoring nonusers^{24,82,106}, and one¹⁴ exhibiting a trend toward larger volume in users but did not reach significance. In the UK Biobank (UKB) cohort, MHT use did not modify the age–brain-volume relationship.⁹⁰ White matter volume (WMV) was more consistently null than GMV, with no difference by MHT status in two cross-sectional studies.^{76,82}

Endogenous hormones

One cross-sectional study found that higher serum estrone was associated with lower total cerebral brain volume, but mainly among women aged ≥ 60 years.¹³ Two longitudinal cohort studies of global volume were conducted in men and both showed null results. Testosterone concentrations measured in young men in adulthood were not associated with midlife (10–15 years later) total brain volume in CARDIA, although higher SHBG predicted greater total WMV.¹⁰⁷ Similarly in a study of WWII veteran twins, midlife (10–16yrs later) testosterone, estradiol, estrone and SHBG were unrelated to later total brain volume.⁵¹

Menopause status

Five cross-sectional and one cohort study reported on this association. Results for menopausal status and age at menopause and global brain volume were heterogeneous. In large cross-sectional UKB analyses, postmenopausal women had smaller total brain, GMV, and WMV than pre/perimenopausal women, and the negative cross-sectional association between age and volume was steeper after menopause.⁹⁰ Similarly, in a Korean sample, Kim et al.¹⁰⁵ found lower total GMV and WMV in postmenopausal than premenopausal women, although the groups differed substantially in age. A graded pre- > peri- > postmenopausal pattern was observed where reproductive stage was modelled ordinally.¹⁴ In a longitudinal study including the UKB cohort, with one MRI measure, menopause before age 50 was associated with lower global GMV and WMV relative to menopause at age 50 or later.¹²

Findings for age at menopause were discordant showing that later menopause was associated with smaller total brain volume within postmenopausal women in UKB,¹⁰³ whereas earlier versus later natural menopause was unrelated to total brain, GM, WM, or intracranial volume in a sample of 35 women.⁸⁶

Reproductive and parity-related factors

Parity was associated with larger global GMV in a cross-sectional Rotterdam Study but was not associated with WMV after full adjustment.⁷⁴ McGrath et al.¹³ similarly reported that women with at least three live births had greater total cerebral brain volume than women with no live births. However, evidence on menarche and reproductive span are contradictory, with one cross-sectional UKB study showing that later menarche was associated with larger, and longer reproductive duration with smaller, total brain volume in UK Biobank,¹⁰³ whereas earlier menarche was associated with lower total cerebral brain volume in the Framingham study.¹³

Other female-specific factors

Women with PCOS did not differ from women without PCOS in WMV in the CARDIA MRI subset,⁹³ and hysterectomy without oophorectomy showed only nonsignificant trends toward smaller global gray and white matter volume.¹⁴

Regional and lobar gray-matter and white-matter volumes and morphology

There were 21 studies with regional and lobar GMV and WMV outcomes, of which 14 were cross-sectional studies,^{9,14,15,25,44,52,74,87,104–106,108–110} four were cohort studies,^{51,96,107,111} and three RCTs^{18,23,99}. Most regional studies were cross-sectional and used voxel-based morphometry, atlas-derived lobar volumes, or manually delineated regions.

Exogenous hormone exposure

Three cross-sectional studies (n ranging from 41–562) found MHT use associated with larger regional volumes,^{9,104,106} including frontal, prefrontal, parietal, temporal, occipital, cerebellar, and hypothalamic regions, and relative medial-temporal white-matter sparing among MHT users. Two of these studies also

reported longer treatment being associated with greater regional tissue sparing,^{104, 106} Schelbaum et al.¹⁵ reported larger regional GMVs with MHT and hormonal-contraceptive use in frontal, temporal, precuneus, parietal, angular, and fusiform regions.

Three cross-sectional studies found adverse or null associations. Sullivan et al.¹⁰⁹ found no meaningful regional or global tissue-volume differences by treatment status. Rahman et al.¹⁴ observed only nonsignificant trends toward larger regional GMV and WMV in MHT users. Ryan et al.,⁸⁷ in a cross-sectional population-based study, found no difference in midsagittal corpus callosum area between current or past MHT users and women who had never used MHT.

In a five-year repeated-measure MRI study, Raz et al.¹¹¹ found significant shrinkage of the lateral prefrontal cortex, fusiform cortex, and prefrontal WM in controls, whereas no eligible region significantly declined among MHT users. This study included only 12 women per group. These cross-sectional and cohort studies used non-randomized self-reported or clinically judged MHT, reducing the certainty in the MHT classification and increasing confounding.

In the ancillary WHIMS-MRI RCT studies, women previously assigned to CEE-based therapy had lower frontal lobe volumes than placebo-treated women,²³ and MHT-assigned women had smaller frontal lobe volumes overall approximately 6–7 years after trial completion, though without accelerated annual regional volume loss between scans.¹⁸ Espeland et al.⁹⁹ found no frontal lobe difference across treatment arms among women with cognitive impairment four years after the trial concluded.

Endogenous hormones and gonadotropins

One Korean cross-sectional study of 41 pre- and post-menopausal women, found positive associations of estradiol with supplementary motor, inferior frontal, and superior temporal GMVs and inverse associations of FSH with several of these regions,¹⁰⁵ while another Korean study of 41 menopausal MHT users and nonusers, found that FSH, LH, and progesterone showed negative associations with selected regional volumes.¹⁰⁶ A Chinese study of 57 pre- and post-menopausal women found no significant associations of FSH and LH with pallidal volume.¹⁰⁸ In a larger US sample, endogenous estradiol and estrone were largely unassociated with regional volumes, with isolated positive associations for left caudal middle frontal (both) and fusiform (estrone) volumes; associations were stronger where plasma AD biomarker profiles were more favorable and were largely restricted to APOE ε4 noncarriers.¹¹⁰ Higher plasma SHBG was associated with lower temporal lobe volume in participants with MCI but not in cognitively normal or AD participants.⁵²

In longitudinal cohort studies of men, higher midlife testosterone was associated with larger later bilateral hemispheric, frontal, and parietal volumes, but smaller left occipital volume.⁵¹ Higher estradiol and estrone were associated with smaller occipital volumes. Elbejjani et al.¹⁰⁷ found that higher SHBG was associated with smaller parietal GMV and greater total WMV; testosterone was not associated with the regional volumes.

Menopause status

There were six cross-sectional studies that reported menopause status and regional/lobar brain GMV and WMV. Perimenopausal and postmenopausal women had lower frontal gray and WMVs than premenopausal controls, following a control > perimenopause > postmenopause gradient.⁴⁴ Postmenopausal women had lower inferior temporal GMV and lower anterior and posterior corona radiata WMV, while perimenopausal women had lower precuneus and fusiform volumes than postmenopausal women.²⁵ Perimenopausal women had lower volume in the putamen, pallidum, inferior parietal, superior frontal and postcentral regions;¹⁰⁸ postmenopausal women had lower volume in the supplementary motor area, inferior frontal gyrus, olfactory cortex and superior temporal gyrus after age adjustment.¹⁰⁵ Peri/postmenopausal status was associated with lower inferior temporal GMV.¹⁵ One study was entirely null, reporting no difference in temporal lobe GMV and WMV across premenopausal women, postmenopausal nonusers and postmenopausal MHT users in a sample of 44 healthy women.¹⁰⁹

Reproductive and parity-related factors

Parity was associated with larger regional gray matter volume across temporal, frontal, occipital and parietal cortices.¹⁰⁹ Greater numbers of children or pregnancies were associated with larger frontal and temporal volumes, and longer reproductive span with larger parietal and precuneus volumes, whereas age at menarche was unrelated to GMV; in men, number of children was not associated with GMV.¹⁵

Other female-related factors

Two cross-sectional studies found no clear association between hysterectomy status and regional GMV or WMV, although hysterectomy status was operationalized differently across.^{14,15} Rahman et al.¹⁴ examined hysterectomy status as a predictor of AD-related neuroimaging biomarkers in a mixed sample of premenopausal, perimenopausal, and postmenopausal women, while Schelbaum et al.¹⁵ assessed menopause type as a categorical variable comparing spontaneous menopause with induced menopause, defined as hysterectomy and/or oophorectomy before menopause.

One cohort study, with a median of 11 years after pregnancy reported that women with prior hypertensive disorders of pregnancy did not differ from controls in regional GMV.⁹⁶

Cortical thickness, cortical surface area, cortical volume/morphology, and cortical atrophy-pattern measures

A total of 12 studies reported cortical outcomes, including seven cross-sectional studies,^{11,13,71,90,112–114} three cohort studies,^{12,63,96} and two RCTs.^{20,22} Most studies used a single MRI and therefore measured cortical morphology rather than cortical thinning over time.

Exogenous hormone exposure

Among cross-sectional studies, Zuhlsdorff et al.¹¹⁴ found lower anterior-cingulate GMV among postmenopausal ever-MHT users than nonusers in the UKB. In the Framingham Offspring cohort, postmenopausal MHT use was associated with a lower MRI Alzheimer's disease and related dementias (ADRD) signature score, indicating greater atrophy across AD-typical cortical regions, among women aged ≥ 60 years.¹³

In a longitudinal cohort study of community-dwelling older women, Lee et al.⁶³ found that prior hormonal contraceptive use was associated with greater longitudinal cortical thickness in an AD temporal meta-region of interest (ROI). MHT initiated before or within one year after menopause was associated with greater cortical thickness at the index assessment compared with nonuse, but not with slower subsequent thinning, and ever-MHT use was not associated with change in thickness.⁶³

Two RCTs that come from KEEPS showed that the earlier positive signal did not persist. At 84 months, transdermal estradiol was associated with preservation of dorsolateral, superior and middle frontal cortical volumes relative to placebo, whereas oral CEE showed no effect across the 21 cortical regions of interest examined.²² Approximately 10 years after the trial ended, however, neither original treatment assignment was associated with dorsolateral prefrontal cortical thickness.²⁰

Endogenous hormones and gonadotropins

Estrogen and estradiol concentrations were positively correlated with surface area in the left medial orbitofrontal, right lateral orbitofrontal and right superior temporal cortices, and with right anterior pulvinar volume in a cross-sectional Korean study.¹¹² On the AD cortical signature measure, higher serum estrone was cross-sectionally associated with a lower MRI ADRD signature score among women aged ≥ 60 years.¹³

Menopause status

Postmenopausal women had smaller surface area in the left medial orbitofrontal, right lateral orbitofrontal and right superior temporal cortices, with no other cortical region surviving Bonferroni correction.¹¹² In UKB, postmenopausal women showed steeper age-related decline than pre/perimenopausal women across the frontal, temporoparietal, occipital, opercular and paracingulate cortices, and MHT use did not modify this association;⁹⁰ a separate UKB analysis found lower anterior cingulate cortex GMV in postmenopausal than premenopausal women.¹¹⁴ One study reported null results, showing that inferior parietal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex volumes did not differ by menopause stage in a US midlife sample.¹¹³

One UKB cohort study, following 11,604 women over a median of 8.8 years, reported that earlier menopause (< 50 years) was associated with lower volume and lower cortical thickness across most cortical regions, including the frontal, parietal and temporal cortices.¹² While another longitudinal study

using the Mayo Clinic Study of Aging, found that age at menopause was not associated with change in AD temporal meta-ROI cortical thickness.⁶³

Reproductive and parity-related factors

One cross-sectional study found that having ≥ 3 live births was associated with a higher MRI ADRD signature score, indicating less atrophy across AD-typical cortical regions, compared with no live births.¹³ Earlier menarche was associated with lower total cerebral brain volume in the same study, but its association with the signature score itself was not reported.

A cohort study reported age at menarche, reproductive window length and other reproductive factors were not associated with change in AD temporal meta-ROI cortical thickness.⁶³

Other female-specific factors

In a longitudinal pregnancy study, with one MRI approximately 11 years after delivery, prior hypertensive disorders of pregnancy or preeclampsia were not associated with cortical thickness.⁹⁶

Kantarci et al.¹¹ found that oophorectomy before age 46 was associated with a thinner entorhinal cortex and an increasingly thinner Alzheimer-like temporal cortical pattern at older imaging ages in a cross-sectional study. However, oophorectomy at ages 46–49 was not associated with these outcomes. Zeydan et al.⁷¹ similarly found cross-sectionally a thinner parahippocampal-entorhinal cortex among women who underwent premenopausal bilateral salpingo-oophorectomy.

Ventricular enlargement, CSF measures, and other indices of atrophy

There were 13 studies with either ventricular enlargement, CSF measures, and other indices of atrophy as an outcome. There were eight cross-sectional studies,^{13,70,76,77,82,83,85,87} one cohort study,⁹⁷ and four RCTs.^{18,22,23,101} The measures varied substantially. Older studies used visual ventricular and sulcal ratings, bifrontal distance, or CSF proportions; later studies used automated segmentation, boundary-shift integral methods, repeated ventricular measurements, or machine-learning atrophy signatures. Consequently, the outcomes should not be treated as interchangeable measures of the same biological process. Two of the RCTs^{18,23} arose from the overlapping WHIMS-MRI population, whereas the other two^{22,101} measured ventricular volume and whole brain change during and after randomized treatment in the KEEPs.

Exogenous hormone exposures

The findings were especially heterogeneous. In the Cardiovascular Health Study, current MHT users had greater bifrontal distance and higher ventricular-size grades than past and never users but did not differ in sulcal widening. Treatment duration was unrelated to atrophy measures.⁸³ Greenberg et al.⁷⁶ found greater nonventricular CSF but no difference in ventricular CSF among long-term users. Ryan et al.⁸⁷

found a higher CSF-to-intracranial-volume ratio, indicating more global atrophy, among current users than never-users. Low et al.⁸² found no treatment-group difference in global or regional atrophy indices.

Longitudinal observational and randomized results also varied. In a very small longitudinal cohort, MHT users had less progression of total, anterior, and posterior ventricular CSF over approximately 3.7 years than nonusers.⁹⁷

In KEEPS, oral-CEE produced greater ventricular expansion during four years of randomized treatment than placebo; transdermal estradiol showed a numerically similar but nonsignificant difference. Whole-brain-volume decline did not significantly differ by treatment.¹⁰¹ Three years after treatment ended, the excess ventricular expansion in the oral-CEE group was no longer distinguishable from placebo.²²

In WHIMS, ventricular volume did not differ on the first post-trial MRI between CEE-treated and placebo groups,²³ and prior treatment did not influence subsequent annual ventricular expansion during the repeat-MRI interval.¹⁸

Endogenous hormones

In older Japanese-American men, higher bioavailable testosterone was associated with greater cerebral atrophy, and a positive association with bioavailable estradiol was attenuated after adjustment for testosterone.⁷⁷ The analysis was cross-sectional with respect to MRI and used hormones measured approximately three years earlier.

Parity and other female-specific factors

Grand multiparity (defined as at least five deliveries) was associated with more adverse Alzheimer- and brain-aging-pattern atrophy indices than zero to four deliveries.⁷⁰ Conversely, McGrath et al.¹³ found a more favorable ADRD cortical signature among women with at least three live births than women with none.

Women with a history of hypertensive pregnancy disorders had greater MRI-defined brain atrophy decades later than women with normotensive pregnancies, whereas ventricular volume did not differ significantly.⁸⁵

Hippocampal volume

Twenty-four studies examined hippocampal volume in the included studies. The majority of studies used a cross-sectional design (n = 18),^{13,17,19,54,70,71,77,82,87,95,103,109,114–119} followed by RCTs (n = 4),^{16,18,20,23} and three studies used a longitudinal design (n = 3).^{35,54,111} One study contributed both cross-sectional and longitudinal data,⁵⁴ thus the study design counts exceed the number of included studies. Studies were primarily conducted in the USA (n = 14),^{13,16–18,20,23,35,54,71,77,109,111,118} followed by the United Kingdom (n = 4),^{95,103,114,119} and Canada (n = 2).^{54,116} One study each was conducted in Australia,⁸²

China,⁵⁴ France,⁸⁷ Norway,¹¹⁷ South Korea,⁷⁰ and the Netherlands.¹⁹ When exposures were counted across all relevant categories, MHT was the most frequently investigated exposure (n = 15),^{13,16–18,20,23,82,87,95,111,115–119} followed by hormones and gonadotropins (n = 4).^{13,19,54,77} Four studies examined parity/reproductive factors,^{13,70,103,119} four examined menopause status^{35,103,109,114} and one examined gynecological conditions and reproductive surgery.⁷¹ Four studies used data from the UK Biobank (UKB),^{95,103,114,119} and two were based on WHIMS and its ancillary studies.^{18,23} The total analytical sample size ranged from 12 to 19,846 participants.

Exogenous hormone exposure

Across cross-sectional studies, evidence regarding MHT and hippocampal volume was inconsistent. Three studies reported positive findings,^{17,115,117} whereas six reported no significant associations^{13,87,119} or group differences.^{82,116,118} Current MHT users (n = 13) had larger right hippocampal volumes than non-users (n = 46) and larger anterior hippocampal volumes than female non-users in a sample of community-dwelling Mexican American older adults without dementia.¹¹⁵ Similarly, peri-/postmenopausal women who initiated HT before menopause and continued use through menopause for ≥ 3 years (n = 80) demonstrated larger right hippocampal volumes and relative sparing of the CA1/subiculum region compared with age- and intracranial volume-matched never-users (n = 80).¹¹⁷ Erickson et al. further reported larger bilateral hippocampal volumes among women who initiated HT at the time of menopause compared with never-users and women who initiated HT later after menopause (1–18 years post-menopause).¹⁷ In contrast, a recent large UKB analyses (N = 19,846) reported smaller bilateral hippocampal volumes in current, but not past, MHT users, with longer duration of use and older age at last use relative to menopause were associated with lower hippocampal volumes.⁹⁵ However, among MHT users, a history of hysterectomy without oophorectomy was associated with larger bilateral hippocampus volumes compared with MHT users without surgical history.⁹⁵ Overall, cross-sectional evidence does not support a consistent beneficial association between MHT and total hippocampal volume, although findings suggest that timing of initiation, duration of exposure, and specific hippocampal subregions may influence observed associations.

Longitudinal evidence did not support a protective effect of MHT on hippocampal volume trajectories. In a 5-year follow-up study of 24 healthy postmenopausal women, both MHT users and age-and-education-matched non-users exhibited significant hippocampal shrinkage over time, and the magnitude of hippocampal volume loss did not differ between groups.¹¹¹ Similarly, another small longitudinal study (N = 31) reported no significant differences in hippocampal volume change among current MHT users, past MHT users, and never users over approximately 3 years of follow-up.¹¹⁸ Overall, the available longitudinal evidence suggests that MHT use was not associated with a reduced rate of hippocampal atrophy in later life.

Evidence from intervention studies was largely null regarding total hippocampal volume. In the WHIMS-MRI trial, women aged ≥ 65 years and older to either CEE with or without MPA had smaller hippocampal

volume compared to placebo when assessed on average 8 years after original WHI enrollment (approximately 3.0 years post-trial cessation for the CEE + MPA trial and 1.4 years post-trial cessation for the CEE-Alone trial), particularly among women with poorer baseline cognitive function and greater ischemic lesion burden.²³ However, subsequent longitudinal follow-up in WHIMS-MRI2 study demonstrated no differences in the rate of hippocampal atrophy between treatment and placebo groups over 4.7 years of follow-up.¹⁸ Similarly, neither oral CEE nor transdermal 17 β -estradiol was associated with hippocampal volume (compared to placebo) approximately 10 years after completion of the KEEPS randomized trial, and no modification by APOE ϵ 4 carrier status was observed.²⁰ In contrast, a prospective intervention study pooling two different clinical trials reported a short-term dose-dependent regional response to estradiol treatment.¹⁶ Although no significant differences were observed in total left or right hippocampal volume after 3 months of treatment, women receiving 2 mg/day 17 β -estradiol demonstrated greater increases in bilateral posterior hippocampal gray-matter volume than women receiving placebo or 1 mg/day estradiol.¹⁶

Overall, intervention studies provide little evidence that MHT preserves total hippocampal volume. Findings were largely null, with reduced hippocampal volumes observed only in the WHIMS-MRI trial among older women initiating CEE-based therapy after age 65 years, whereas subsequent follow-up and other intervention studies reported no effects on total hippocampal volume. The only positive finding was increased posterior hippocampal GMV following short-term 2 mg/day estradiol treatment in relatively younger postmenopausal women (mean age 58 years).¹⁶

Endogenous hormones and gonadotropins

Findings differed according to the hormone examined. For estradiol, all evidence came from cross-sectional studies. Older women (N = 210) in the highest tertiles of total, bioavailable, and free estradiol levels had smaller total hippocampal volumes than those in the lowest tertiles, although continuous total estradiol was not associated with hippocampal volume in the Rotterdam Scan Study.¹⁹ Similarly, serum estradiol concentrations were not associated with total hippocampal volume among cognitively healthy women in the Framingham Heart Study Offspring cohort.¹³ Among older men, neither the Rotterdam Scan Study¹⁹ nor the Honolulu–Asia Aging Study⁷⁷ found any evidence of an association between estradiol and hippocampal volume. No associations between total, bioavailable, or free estradiol and total hippocampal volume were observed among men (N = 202) in the Rotterdam Scan Study,¹⁹ while serum bioavailable estradiol was not associated with hippocampal atrophy (defined as the lowest quartile of hippocampal volume) in older Japanese-American men from the Honolulu–Asia Aging Study (N = 452; mean age 81.6 years).⁷⁷

Evidence for estrone was limited to a single cross-sectional study,¹³ which found no association between serum estrone concentrations and total hippocampal volume among cognitively healthy women.

Similarly, bioavailable testosterone was not associated with hippocampal atrophy in older Japanese-American men from the Honolulu–Asia Aging Study.⁷⁷

For SHBG, findings differed by study design. Serum SHBG was not associated with hippocampal atrophy in a cross-sectional analysis of older Japanese-American men from the Honolulu–Asia Aging Study,⁷⁷ whereas higher plasma SHBG levels were associated with faster hippocampal atrophy over time in older adults (approximately 63% men) from the ADNI cohort (N = 188).

Menopause status

Four studies examined menopausal status and hippocampal volume,^{35,103,109,114} two of which were based on UKB data.^{103,114} A study of 44 healthy women found no significant differences in hippocampal volume between premenopausal women, postmenopausal women using MHT, and postmenopausal women not using MHT.¹⁰⁹ The two UKB studies showed differing findings. Ambikairajah et al.¹⁰³ reported that postmenopausal women had larger total hippocampal volume than premenopausal women among 5,072 who had never used MHT, and this association remained significant in a propensity score-matched sensitivity analysis. In contrast, Zuhlsdorff et al.¹¹⁴ found that, in a sample of 10,873 women, postmenopausal women had lower hippocampal gray matter volumes than premenopausal women, with the lowest volumes observed among postmenopausal women who had used HRT. However, the authors note that women prescribed MHT may have differed from non-users prior to treatment, and post-hoc analyses suggesting higher levels of pre-existing mental health symptoms among future MHT users, indicating possible confounding by indication.¹¹⁴ One longitudinal study found that menopausal women compared with peri- or pre-menopausal women had greater hippocampal volume loss over approximately three years.³⁵ However, this cohort study had a limited sample size (n = 41) and menopausal status was not hormonally confirmed.³⁵ Overall, findings regarding menopausal status and hippocampal structure are inconsistent.

Reproductive and parity-related factors

Overall, the literature examining parity and hippocampal volume is limited and yields mixed findings. In a cohort of older women with normal cognition or MCI, grand multiparity (≥ 5 births) was associated with smaller hippocampal volumes compared with women who had 0–4 births.⁷⁰ In contrast, a community-based study of women without dementia found no association between the number of live births (0 [reference], 1–2, and ≥ 3) and hippocampal volume.¹³

Three cross-sectional studies examined age of menarche, age of menopause, and reproductive span,^{13,103,119} of which two derived data from the UKB.^{103,119} In women without dementia (mean age 60.4 [9.4]), age at menarche and reproductive lifespan were not associated with total hippocampal volume.¹³ However, earlier menopause (≤ 49 years) was associated with lower hippocampal volume compared with menopause occurring at 50–51 years, whereas later menopause (≥ 52 years) showed no significant association with hippocampal volume.¹³

For age of menarche, both UKB studies reported no significant association with hippocampal volume.^{103,119} In contrast, findings for age at menopause were inconsistent. Ambikairajah et al.¹⁰³ reported that later menopause was associated with smaller hippocampal volume among 4,337 postmenopausal women without previous MHT use, whereas Steventon et al.¹¹⁹ in 10,924 postmenopausal women, found that later menopause was associated with larger hippocampal volume and larger volumes in the CA4 and dentate gyrus subfields. Similarly, findings for reproductive span differed between studies. Ambikairajah et al.¹⁰³ found no significant association between reproductive-stage duration and hippocampal volume, whereas Steventon et al.¹¹⁹ reported that a longer reproductive span was associated with larger hippocampal volume, particularly in the CA4 and dentate gyrus subfields. These contrasting findings might reflect differences in sample selection, inclusion criteria, and analytical approaches.

Gynecological conditions and reproductive surgery

In a cross-sectional study of 43 community-dwelling women, those who underwent BSO before age 50 and prior to natural menopause exhibited smaller hippocampal volumes than age-matched controls; however, this difference was not statistically significant.⁷¹

Nonhippocampal subcortical and medial-temporal regional volumes

There were 12 studies, of which 11 were cross-sectional,^{10,17,71,76,82,90,108,112,116,119,120} and one was a cohort study.¹²

The outcomes included the amygdala, caudate, putamen, pallidum, thalamus or thalamic nuclei, brainstem, parahippocampal cortex, perirhinal cortex, and entorhinal cortex.

Exogenous hormone exposures

Several studies reported null subcortical results. Timing of MHT initiation was not associated with amygdala or caudate volume in Erickson et al.¹⁷ Amygdala volume did not differ between MHT current users, past users, and never-users in a study by Lord and colleagues.¹¹⁶ Greenberg et al.⁷⁶ found that caudate and putamen differences did not survive correction for multiple comparisons, and Low et al.⁸² found no amygdala-volume difference by treatment status.

Longer MHT duration was associated with larger parahippocampal volume in Steventon et al.,¹¹⁹ but not consistently with the other nonhippocampal medial-temporal structures examined (i.e., perirhinal and amygdala volumes).

Menopause status

Early menopausal women had smaller bilateral amygdala volumes than age-matched premenopausal women.¹²⁰ In the cross-sectional UKB analysis by Steventon et al.¹¹⁹ including 10,924 postmenopausal

women, earlier natural menopause and a shorter reproductive span were associated with smaller amygdala, parahippocampal, and perirhinal volumes. Another cross-sectional UKB⁹⁰ study of 230 pre/perimenopausal and 1,827 postmenopausal women, found that the inverse association between age and the bilateral putamen volume was steeper in pre/perimenopausal than postmenopausal women.

Other subcortical regions were also implicated. Lu et al.¹⁰⁸ found lower putamen and pallidum gray-matter volume during perimenopause. Kim et al.¹¹² found a smaller right anterior pulvinar after menopause, although total right-thalamic volume was not significant after multiple-comparison correction. Liao et al.¹² reported over a median of 12.3 years smaller thalamic, basal-ganglia, and brainstem measures in association with menopause before age 50, in the UKB cohort.

Other female-specific factors

In a cross-sectional study from the Mayo Clinic of 43 participants, women with premenopausal bilateral salpingo-oophorectomy had smaller amygdala volumes than controls.⁷¹ While a cross-sectional Canadian study of 85 women found that medial temporal cortical volumes did not differ between women with BSO, those with BSO and taking MHT, or age-matched controls.¹⁰

Discussion

This systematic review evaluated associations between female- and male-specific reproductive and hormonal factors and AD-related biomarkers across the AT(N) framework. Overall, the evidence suggests that reproductive and hormonal factors may influence several AD-related biomarkers and neuroimaging outcomes, but findings were highly heterogeneous across exposures, biomarkers, population and study designs. The strongest and most consistent signals emerged for menopausal transition, gonadotropins (particularly FSH), early reproductive factors, and selected female-specific conditions such as hypertensive pregnancy disorders, vasomotor symptoms, and premenopausal oophorectomy. In contrast, evidence for MHT, endogenous sex steroid hormones, parity, and reproductive lifespan was generally inconsistent, with few associations replicated across studies.

A notable finding across the reviewed literature was that associations between reproductive and hormonal factors and AD biomarkers were substantially more evident in women than in men. This likely reflects both the greater number of studies examining female-specific reproductive exposures and the profound endocrine changes accompanying the menopausal transition. Most evidence relating reproductive and hormonal factors to amyloid deposition, cerebral glucose metabolism, structural brain measures, and white-matter integrity was derived from female cohorts.

Among women, the most consistent findings were observed for markers of reproductive aging. Menopausal transition and earlier menopause were repeatedly associated with less favorable biomarker profiles, particularly for amyloid accumulation, cerebral glucose metabolism, cortical and subcortical brain structure, and white-matter integrity. Several studies reported higher amyloid burden among peri-

and postmenopausal women compared with premenopausal women, and longitudinal evidence suggested greater amyloid accumulation following menopause. Earlier menopause was also associated with smaller global and regional brain volumes, thinner cortices, and greater white-matter abnormalities in several cohorts.

The evidence for circulating reproductive hormones suggested that gonadotropins may be particularly important. Higher FSH concentrations were consistently associated with greater amyloid pathology in women, whereas estradiol levels were generally not associated with amyloid or tau biomarkers. Findings for LH were mixed. These observations suggest that endocrine changes accompanying ovarian aging may be more strongly related to AD-related brain changes than absolute estrogen concentrations alone.

Female-specific conditions also showed relatively consistent associations with adverse brain outcomes. Hypertension during pregnancy, objectively measured vasomotor symptoms, and premenopausal bilateral oophorectomy were associated with less favorable biomarker profiles across multiple studies, including greater amyloid burden, increased white-matter abnormalities, or more pronounced neurodegenerative structural changes. These findings support the concept that reproductive health events occurring across the life course may contribute to later-life brain vulnerability.

In contrast, evidence regarding MHT was inconsistent. Although some cross-sectional studies suggested lower tau burden, lower amyloid burden, higher glucose metabolism, or larger regional brain volumes among users, most longitudinal studies and randomized trials failed to demonstrate consistent protective associations. Collectively, the evidence suggests that MHT is not uniformly associated with reduced AD pathology, although treatment timing, formulation, and APOE ϵ 4 status may influence outcomes.

Compared with women, the evidence in men was considerably more limited and generally less consistent. Most male-focused studies investigated endogenous sex hormones rather than reproductive history. Testosterone findings varied across biomarker domains. Lower testosterone levels were associated with greater amyloid burden in some studies and higher CSF p-tau181 concentrations in another, but several studies reported no associations. Similarly, evidence for estradiol was largely null across amyloid, hippocampal, and structural MRI outcomes.

SHBG emerged as the hormonal marker most consistently associated with adverse brain outcomes in men. Higher SHBG levels were linked to less favorable amyloid biomarkers, faster hippocampal atrophy, lower temporal lobe volume, and greater decline in glucose metabolism in some studies. However, not all findings were replicated across cohorts.

Overall, male-specific evidence was sparse and lacked the consistency observed for female reproductive aging factors. Whereas women showed relatively coherent associations between menopause-related processes and multiple AD biomarker domains, findings in men were largely limited to isolated associations involving testosterone and SHBG and did not reveal a similarly consistent pattern across amyloid, tau, neurodegeneration, and cerebrovascular outcomes.

The pattern of associations differed substantially across biomarker categories. Amyloid pathology demonstrated the largest evidence base and generally showed the most consistent associations with menopausal transition, elevated FSH, and some female-specific conditions. Multiple studies suggested greater amyloid burden among perimenopausal, and postmenopausal women compared with premenopausal women, particularly among APOE ϵ 4 carriers, and longitudinal evidence indicated greater amyloid accumulation after menopause.

By contrast, evidence for tau pathology was substantially weaker and less consistent. Most associations were cross-sectional, and longitudinal studies were overwhelmingly null. Although some studies suggested greater tau burden among women with earlier menopause, late MHT initiation, elevated amyloid burden, or premenopausal oophorectomy, findings lacked consistency across cohorts and biomarker modalities.

Markers of neurodegeneration and neuronal injury, including FDG-PET, brain volumes, cortical morphology, hippocampal volume, and NfL, showed an intermediate level of evidence. Menopausal transition was consistently associated with lower cerebral glucose metabolism in AD-vulnerable regions and with lower regional brain volumes in several cohorts. Earlier menopause and surgical menopause were also repeatedly linked to less favorable structural brain outcomes. In contrast, NfL evidence was limited and uniformly null across the few available studies.

Associations were also relatively consistent for cerebrovascular and white matter outcomes. Earlier menopause, elevated FSH, hypertensive pregnancy disorders, objectively measured vasomotor symptoms, PCOS, and premenopausal oophorectomy were repeatedly associated with greater WML burden or poorer white matter integrity. In contrast, evidence linking MHT to white matter outcomes was largely null across observational studies and randomized trials.

Strengths and limitations of the evidence base

Several limitations of the available literature should be considered when interpreting the findings of this review.

First, the evidence base was dominated by cross-sectional studies, with relatively few longitudinal investigations and randomized controlled trials. Consequently, temporal relationships between reproductive or hormonal exposures and AD-related biomarkers remain uncertain, limiting causal inference and raising the possibility of reverse causation. For many exposures, particularly reproductive history, endogenous hormones, and female-specific health conditions, conclusions were primarily based on cross-sectional associations.

Second, there was substantial heterogeneity in exposure assessment. Reproductive and hormonal factors were often measured using self-reported questionnaires, retrospective recall, or medical records, and definitions varied considerably across studies. Menopausal status was classified using different approaches (e.g., self-report, STRAW criteria, clinical judgment, hormone measurements), while MHT

exposure varied according to formulation, route of administration, dose, timing of initiation, duration, and recency of use. Similarly, endogenous hormone studies differed in specimen type, assay methods, timing of sample collection, and adjustment for relevant biological factors, limiting comparability across studies.

Third, there was marked heterogeneity in biomarker ascertainment and outcome definitions. Studies used a wide range of AD-related biomarkers, including PET imaging, CSF biomarkers, plasma biomarkers, structural MRI, diffusion imaging, FDG-PET, and NfL. Even within biomarker domains, outcome definitions varied considerably. For example, amyloid outcomes included global and regional PET burden, CSF A β 42, A β 42/A β 40 ratios, plasma biomarkers, and amyloid positivity classifications. White-matter outcomes ranged from visual ratings to automated lesion volumes and diffusion-based microstructural measures. This heterogeneity precluded direct comparison of findings and may partly explain inconsistent results.

Fourth, many studies were based on highly selected cohorts, including individuals with elevated AD risk, family history of dementia, APOE ϵ 4 enrichment, participants enrolled in aging studies, memory clinic populations, or relatively healthy volunteers. As a result, findings may not be generalizable to broader populations. In addition, many cohorts were composed predominantly of White participants from North America or Europe, with limited representation of diverse racial, ethnic, socioeconomic, and geographic populations.

Fifth, overlapping cohorts were common, particularly for studies derived from ADNI, UK Biobank, WHIMS, KEEPS, Framingham Heart Study, WRAP, and the REP. Consequently, the apparent volume of evidence may overstate the number of truly independent populations contributing to particular findings. Biomarker associations observed in one cohort may therefore disproportionately influence the overall literature.

Sixth, many studies had small sample sizes, particularly neuroimaging studies, hormone studies, and intervention studies. Several analyses included fewer than 100 participants, limiting statistical power and increasing the risk of both false-positive and false-negative findings. Small sample sizes also restricted the ability to evaluate important interactions, including effects modified by APOE genotype, sex, menopausal timing, or biomarker status.

Seventh, there was considerable potential for residual confounding and confounding by indication, particularly in observational studies evaluating MHT. Women who use hormone therapy may differ systematically from non-users with respect to education, socioeconomic status, cardiovascular health, healthcare access, symptom severity, and underlying health characteristics. Although most studies adjusted for key covariates, the extent and consistency of adjustment varied substantially. Likewise, surgical exposures such as hysterectomy or oophorectomy often occur in the context of underlying gynecological conditions that may independently influence brain health.

Eighth, relatively few studies adequately addressed the timing hypothesis of hormone exposure. Evidence suggests that age at menopause, age at MHT initiation, duration since menopause, and timing

of exposure relative to reproductive transition may be important determinants of associations with AD biomarkers. However, these factors were inconsistently measured and reported, limiting the ability to determine critical windows of vulnerability or benefit.

Ninth, there was evidence of multiple testing and selective reporting concerns. Several studies examined numerous biomarkers, brain regions, reproductive exposures, and interaction terms, sometimes with limited correction for multiple comparisons. Some positive findings were attenuated after adjustment for multiple testing, suggesting that chance findings may contribute to the literature.

Finally, relatively little evidence was available regarding male reproductive and hormonal factors, despite growing interest in sex differences in AD pathophysiology. Most studies focused on women, and male-specific findings were largely restricted to testosterone, estradiol, LH, FSH, and SHBG. Consequently, the evidence base remains insufficient to draw firm conclusions regarding reproductive endocrine influences on AD biomarkers in men.

These limitations indicate that the current evidence base remains heterogeneous and largely observational. Future research would benefit from standardized exposure definitions, harmonized biomarker outcomes, larger and more diverse populations, repeated biomarker assessments, and adequately powered longitudinal studies capable of evaluating critical timing effects and sex-specific mechanisms

Strengths and limitations

To our knowledge, this systematic review is the first to provide a comprehensive synthesis of the evidence examining associations between female- and male-specific reproductive and hormonal factors and AD-related biomarkers. This review has several notable strengths. The protocol was prospectively registered in PROSPERO; the search strategy was developed on consultation with experienced librarians, and no geographical or date restrictions were applied. We adhered to PRISMA guidelines to ensure a systematic, transparent, and reproducible review process, and all study selection, data extraction, and risk-of-bias assessments were conducted independently by two reviewers.

Nevertheless, some limitations should be considered when interpreting the findings. The exclusion of gray literature and non-English peer-reviewed publications may have resulted in the omission of relevant studies, particularly those conducted in low- and middle-income countries, thereby limiting the global representativeness of the evidence. In addition, studies that focused primarily on interactions involving APOE genotype may have been excluded if they did not report overall associations between reproductive or hormonal factors and AD-related biomarkers. We were unable to thoroughly evaluate sources of heterogeneity across studies because of substantial variation in study populations, exposures, biomarker outcomes, and analytical approaches. Consequently, the available evidence was not sufficiently comparable to permit quantitative synthesis through meta-analysis, and findings were therefore summarized narratively.

Conclusion

Taken together, these findings suggest that reproductive aging, rather than exogenous hormone use alone, may be more consistently associated with AD-related biological changes. The transition through menopause, elevated gonadotropin levels, and conditions reflecting abrupt or adverse reproductive aging appear most strongly linked to amyloid deposition, neurodegeneration-related brain changes, and cerebrovascular pathology. However, the predominance of cross-sectional studies, substantial cohort overlap, variability in exposure definitions and biomarker assessments, and limited longitudinal evidence restrict causal inference. Future studies should prioritize longitudinal designs, repeated biomarker assessment, standardized reproductive exposure characterization, and investigation of effect modification by APOE genotype, timing of hormonal exposures, and race/ethnicity to clarify the role of reproductive and hormonal factors in AD pathogenesis.

Abbreviations

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRD	Alzheimer's disease and related dementias
APOE	Apolipoprotein genotype
BSO	Bilateral salpingo-oophorectomy
CEE	Conjugated equine estrogen
CMRglc	Cerebral metabolic rate of glucose
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
ERT	Estrogen replacement therapy
FA	Fractional anisotropy
FDG-PET	Fluorodeoxyglucose PET
FHS	Framingham Health Study
FSH	Follicle-stimulating hormone
GMV	Gray matter volume
HRT	Hormone replacement therapy
HT	Hormone therapy
KEEPS	Kronos Early Estrogen Prevention Study
LH	Luteinizing hormone
MCI	Mild cognitive impairment
MHT	Menopausal hormone therapy
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
oCEE	Oral conjugated equine estrogen
PBO	Premenopausal bilateral oophorectomy
PCOS	Polycystic ovary syndrome
PET	Positron emission tomography
PiB	Pittsburgh compound-B
RCT	Randomized controlled trial

REP	Rochester Epidemiology Project
ROI	Region of interest
SHBG	Sex hormone-binding globulin
STRAW	Stages of Reproductive Aging Workshop
tE2	Transdermal 17 β -estradiol
UKB	UK Biobank
WHIMS	Women's Health Initiative Memory Study
WM	White-matter
WMH	White matter hyperintensity
WML	White matter lesion
WMV	White matter volume
WRAP	Wisconsin Registry for Alzheimer's Prevention

Declarations

Declaration of interests: We declare no competing interests.

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Figures

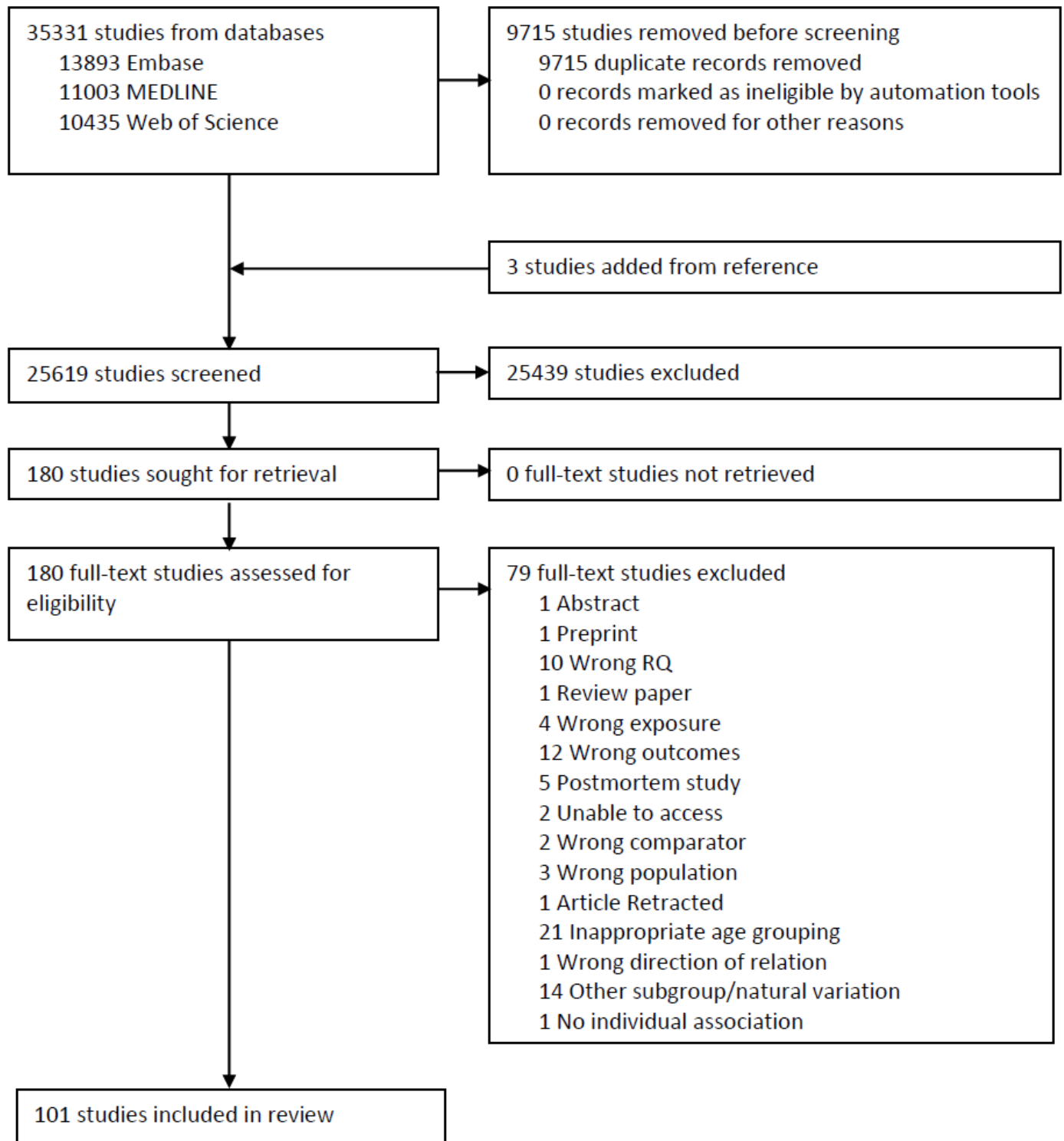


Figure 1

PRISMA flow diagram of study selection process

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