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Hormone Replacement Therapy and Risk of Dementia in Postmenopausal Women: A Systematic Review and Meta-Analysis

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Abstract

Background: *Dementia is a highly prevalent condition with a known predominance in women. Estrogens are hypothesized to exert neuroprotective effects, raising interest in whether menopausal estrogen decline contributes to dementia risk. Consequently, hormone replacement therapy (HRT) has been widely investigated as a potential protective or risk-modifying intervention; however, existing evidence remains conflicting. This systematic review and meta-analysis aimed to evaluate the association between HRT use and the risk of dementia and to explore sources of heterogeneity across studies.*

Methods: *A systematic search of MEDLINE (PubMed) and Scopus was conducted for studies published between January 1990 and May 2025. Randomized controlled trials (RCTs), cohort studies, and case–control studies evaluating estrogen-replacement therapy (ERT) or combined hormone therapy (CHT) in postmenopausal women aged >45 years, with outcomes of all-cause dementia or Alzheimer's disease (AD), were included. Only human studies published in English, German, Portuguese, French, or Spanish were eligible. After screening 5,283 records, 32 studies met the inclusion criteria. Data were qualitatively synthesized, and random-effects meta-analyses were performed, with prespecified subgroup and sensitivity analyses.*

Results: *Thirty-two studies (2 RCTs, 17 cohort studies, and 13 case–control studies) published between 1996 and 2024 were included, with sample sizes ranging from fewer than 200 to over 100,000 participants and follow-up durations from 2 to more than 20 years. In unadjusted analyses, HRT use showed a borderline statistically significant association with lower dementia risk (OR 0.83; 95% CI 0.70–0.99); however, results were highly heterogeneous. In subgroup analyses, estrogen-replacement therapy (ERT) demonstrated a non-significant trend toward reduced dementia risk (OR 0.77; 95% CI 0.59–1.01), whereas no protective association was observed for combined hormone therapy (CHT). Interestingly, effect estimates differed by study design, with observational studies resulting in lower risk and randomized controlled trials indicating increased risk.*

Conclusion: *The available evidence does not support the use of HRT for the prevention of dementia. Observed associations are highly heterogeneous and appear strongly influenced by methodological factors, hormone regimens, and study design. Future research should prioritize well-designed studies with adequate follow-up, standardized diagnostic criteria, and careful consideration of timing, formulation, and confounding variables to better clarify the relationship between HRT and dementia risk.*

Introduction

Dementia is a significant global public health challenge. Its economic burden was estimated at US$ 2.8 trillion in 2019, with a projected rise to US$ 16.9 trillion by 2050 (Lin et al., 2025). Women are at greater risk of developing dementia than men (Gong et al., 2023), influenced by factors such as longer life expectancy, access to education, cardiovascular disease burden, and environmental exposures (Neu et al., 2017; Liao et al., 2023). Estrogens are hypothesized to exert neuroprotective effects (Low & Anstey, 2006). This prompted an investigation into whether menopausal declines in estrogen are linked to dementia risk.

Hormone replacement therapy (HRT) had been widely prescribed for vasomotor symptoms related to menopause. The impact of HRT on cognition may depend on factors such as age, timing, duration, and type of HRT, and the history of surgical hysterectomy or oophorectomy (Nerattini et al., 2023). Previous research on HRT has focused on cardiovascular outcomes; however, effects on cognition remained inconsistent (Gu et al., 2024; Johansson et al., 2024). Multiple observational studies conducted since 1995 identified HRT as a protective factor against the development of dementia, especially in early menopause (Tang et al., 1996; Kawas et al., 1997; Baldereschi et al., 1998; Saleh et al., 2023). However, the largest randomized controlled trial (RCT) evaluating the use of HRT and dementia risk concluded that worse cognitive outcomes were associated with increased age at initiation (Shumaker et al., 2003; Shumaker et al., 2004). These findings supported the "critical window theory," indicating a protective effect of early HRT use. Moreover, methodological limitations in both RCTs and observational studies contributed to the lack of consensus.

The aim of this study is to clarify the extent to which HRT influences dementia risk. We specifically target different HRT regimens not extensively addressed in prior systematic reviews and re-evaluate outcomes using meta-analysis. This dual approach seeks to provide robust and clinically relevant evidence to guide decision-making.

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Materials and Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009).

Eligibility Criteria

Eligibility criteria included postmenopausal women of any age, whether naturally or surgically induced, who received hormone replacement therapy (HRT) and had no prior history of dementia or mild cognitive impairment. Control groups comprised postmenopausal women who had never received HRT or had received non-hormonal therapy or placebo.

The primary outcome of interest was the diagnosis of dementia, major neurocognitive disorder, or Alzheimer's disease. Diagnoses were confirmed using validated instruments such as the DSM or NINCDS-ADRDA criteria, or verified through registries such as ICD codes or neuropathological reports. Diagnoses derived from national health registries were also accepted.

Randomized controlled trials (RCTs) and observational studies were eligible for inclusion. Observational studies encompassed cohort and case-control designs.

Exclusion criteria included publications with cross-sectional or ecological designs, prior dementia diagnoses, and outcomes other than dementia, Alzheimer's disease, or cognitive impairment. Review articles and editorials were also excluded. A detailed outline of the screening process is shown in Figure 1.

Search Strategy

Two electronic databases, MEDLINE (PubMed) and Scopus, were systematically searched between April and May 2025 for studies published from January 1990 to May 2025. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms: "Menopause" OR "amenorrhea" OR "postmenopause" OR "post-menopausal women" OR "perimenopause" OR "Hormone Replacement Therapy" OR "estrogen therapy" OR "HRT" OR "estradiol" OR "progestin therapy" AND "Dementia" OR "Alzheimer's disease" OR "Neurodegenerative diseases" OR "Cognitive decline."

The full search strategy is provided in the Supplementary Material. Only studies conducted in humans and published in English, German, Portuguese, French, or Spanish were included. No time restrictions were applied in the search strategy.

Data Extraction

All retrieved references were imported into Covidence Systematic Review Software.

A total of 5,283 records were identified (Scopus = 3,223; PubMed = 2,060). No additional studies were retrieved from other sources. After removing 1,637 duplicates, 3,646 unique records remained for title and abstract screening, during which 3,307 records were excluded.

The full texts of 339 articles were assessed for eligibility, all of which were successfully retrieved. Following detailed evaluation, 307 studies were excluded for the following reasons: wrong outcomes ($n = 78$), wrong comparator ($n = 1$), wrong article type ($n = 137$), wrong intervention ($n = 14$), inappropriate study design ($n = 49$), full text unavailable ($n = 9$), wrong patient population ($n = 13$), and non-clinical trial articles ($n = 6$). Ultimately, 32 studies met the inclusion criteria and were retained for final analysis.

Screening was conducted independently by two reviewers. Discrepancies were resolved through discussion, and when disagreement persisted, a third reviewer adjudicated. No duplicated or overlapping datasets were identified.

Sensitivity analyses were performed to evaluate the robustness of pooled results by sequentially excluding studies with incomplete or unclear outcome reporting. A detailed summary of the screening process is presented in the PRISMA flow diagram (Figure 1).

Data Synthesis

All included studies were assessed for potential cohort overlap to prevent data duplication. No overlapping cohorts were identified, as each study used a distinct population.

For approximately fifteen studies, participants were stratified according to the type of hormone replacement therapy received to enhance homogeneity and enable more consistent cross-study comparisons. Based on data available from each study, contingency tables were constructed to compare exposures and outcomes and to derive unadjusted odds ratios (ORs).

Meta-analyses were conducted using a random-effects model to estimate pooled effect sizes, and heterogeneity was quantified using the I^2 statistic. Analyses included an overall pooled meta-analysis of all studies, followed by subgroup analyses for combined hormone therapy (CHT) and estrogen replacement therapy (ERT). Effect sizes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

A sensitivity analysis was performed using adjusted effect sizes for the ERT and CHT subgroups when adjusted model results were available. For studies reporting hazard ratios or risk ratios, equivalent OR values were assumed due to the low event rates across studies. Additional subgroup and cumulative meta-analyses were conducted, stratified by study type. Publication bias was evaluated using Egger's test and visually assessed through funnel plots. Finally, sensitivity analyses were performed using a leave-one-out approach.

All statistical analyses were conducted using STATA version 19.5/BE (StataCorp LLC, College Station, TX, USA).

Risk of Bias Assessment

The risk of bias in observational studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS), which evaluates study quality across three domains: selection, comparability, and outcome. The NOS assigns a maximum of nine points for cohort studies and eight points for case–control studies. Based on total scores, studies were categorized as good, fair, or poor quality.

For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool 2 (RoB 2) was applied, which evaluates five domains and classifies studies as having "low risk of bias," "some concerns," or "high risk of bias."

Two reviewers independently conducted all risk of bias and quality assessments. Discrepancies were resolved through discussion, and when necessary, a third reviewer provided a final decision.

Results

Description of the Studies

The present review included information from 14,574,096 subjects distributed across 32 studies, of which two were randomized controlled trials (RCTs), 17 were prospective or retrospective cohort studies, and 13 were case–control studies. The intervention assessed was hormone replacement therapy (HRT) prescribed during the postmenopausal period. Replacement therapy was classified as estrogen replacement therapy (ERT) when the formulation included only estrogen (conjugated equine estrogens or estradiol), and as combined hormone therapy (CHT) when the formulation included any form of estrogen coupled with a progestin (medroxyprogesterone acetate, norethisterone, or micronized progesterone). The route of administration was not considered.

Twenty studies analyzed data on ERT (10 case–control studies, nine cohort studies, and one RCT),

while 13 studies analyzed data on CHT (six case–control studies, six cohort studies, and one RCT). Eleven studies analyzed HRT without distinguishing between subtypes and were labeled as "any HRT." Of the 32 studies included in this review, 12 simultaneously analyzed two different outcomes, one for ERT and another for CHT.

Publication dates ranged from 1996 to 2024. Key contributing countries included the United States, the United Kingdom, Finland, Italy, Denmark, and South Korea. Participant age ranged from 45 to 80 years (overall mean age 67.8 years, SD 10.8). Only 26 studies reported follow-up duration, which ranged from one year to more than 20 years (median 9 years, IQR 5–13 years). Therapy duration ranged from short-term (less than two years) to long-term (over five years). These characteristics are summarized in Table 1.

Quantitative Analysis

Thirty-two studies were included in the meta-analysis, comprising randomized controlled trials (RCTs), cohort studies, and case–control studies. The primary meta-analysis pooled all 32 studies, yielding an unadjusted odds ratio (OR) of 0.83 (95% CI 0.70–0.99), indicating a borderline statistically significant association, with very high heterogeneity (I^2 = 99.7%) (Figure 2). Subgroup analysis by study design showed that cohort studies demonstrated a statistically significant protective association, whereas randomized controlled trials showed a statistically significant increased risk of dementia (case–control OR = 1.09, 95% CI 0.95–1.24; cohort OR = 0.62, 95% CI 0.49–0.69; RCT OR = 1.75, 95% CI 1.18–2.60). Subgroup analyses by type of outcome and by type of HRT used did not result in statistically significant associations (ERT OR = 0.77, 95% CI 0.59–1.01; CHT OR = 0.94, 95% CI 0.64–1.37). These results are presented graphically in the Supplementary Material (Figures S3, S4, and S5). The second model considered adjusted effect sizes reported in the included studies. However, a pooled estimate could not be calculated because 12 studies reported simultaneous outcomes. Therefore, adjusted estimates were analyzed separately for ERT and CHT. For ERT, 20 studies were included, yielding an OR of 0.97 (95% CI 0.86–1.09) (Figure 3). Subgroup analyses of this model showed no significant effects by publication type or outcome type, and leave-one-out meta-analysis indicated a significant influence of the study by Paganini-Hill and Henderson (1996).

The third model included 13 studies and considered only those with CHT as the intervention of interest, resulting in an OR of 1.10 (95% CI 1.03–1.17). Subgroup analysis demonstrated a significant influence of case–control studies and RCTs on this effect. Notably, the case–control subgroup exhibited no heterogeneity, with an I^2 value of 0% (Figure 4).

Cumulative meta-analyses were conducted based on the initial models and stratified by study design. A temporal trend was observed, with older studies demonstrating larger effect sizes, while more recent studies showed estimates closer to the null. This pattern was consistent for both the ERT-only and CHT-only meta-analyses (Figures S5, S6).

Across all models, potential publication bias was assessed using Egger's test ($p = 0.27$) and visual inspection of funnel plots, which did not indicate small-study effects.

Risk of Bias Assessment

Randomized studies included in this review were judged to have low risk of bias or some concerns, primarily related to blinding procedures and participant attrition during long-term follow-up (Supplementary Table 1).

Most observational studies demonstrated acceptable methodological quality (Figures S1 and S2). However, some studies showed risk of bias in the comparability domain, largely due to inadequate adjustment for key confounding variables such as age at HRT initiation, educational level, or comorbidities.

Qualitative Results

Overall, the results were heterogeneous. Several observational studies suggested that initiating hormone replacement therapy (HRT) within 10 years of menopause onset may be associated with a reduced risk of dementia or Alzheimer's disease, particularly when estrogen-only therapy was used in younger women at the time of initiation (Paganini-Hill & Henderson, 1996; Kawas et al., 1997; Whitmer et al., 2011; Kim et al., 2021). These findings support the "critical window" hypothesis, which proposes that the timing of exposure is key to potential neuroprotective effects. In contrast, randomized controlled trials conducted in older women demonstrated that late initiation of any type of HRT was associated with an increased risk of dementia (Shumaker et al., 2003; Shumaker et al., 2004), raising concerns about initiating HRT beyond the age of 65 years.

When disaggregated by type of therapy, estrogen-only therapy (ERT) appeared to have a more favorable cognitive profile compared with combined hormone replacement therapy (CHRT), particularly when initiated early and used for several years. How-

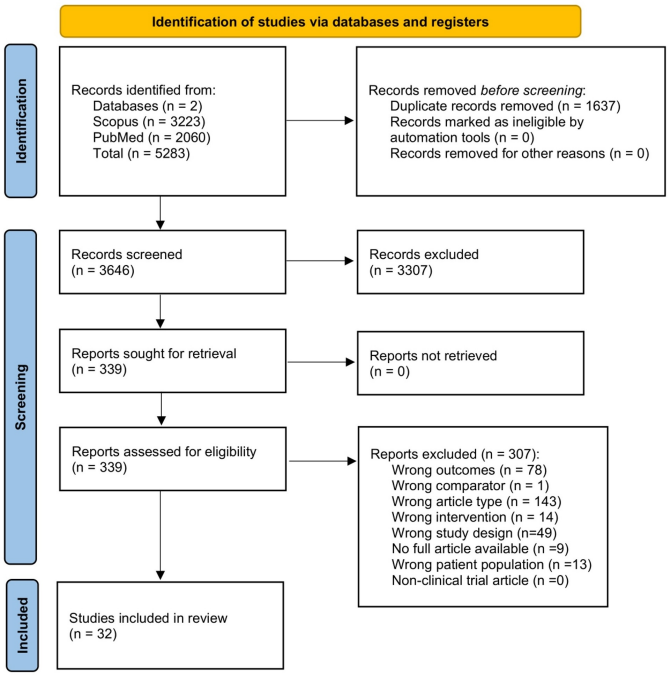

Figure 1: *PRISMA flow diagram.*

ever, findings were inconsistent across studies, and not all observational analyses adequately controlled for key confounders such as educational level, cardiovascular risk factors, or baseline cognitive status.

Duration of use also influenced outcomes. Some studies reported a protective effect associated with long-term use ($\geq$ 5 years), whereas others observed no significant association or an increased risk with prolonged exposure, particularly when therapy was initiated later in life or among women with comorbidities. Taken together, the evidence suggests that the effect of HRT on cognitive outcomes is highly dependent on age at initiation, type of therapy, and duration of use.

Discussion

In our systematic review, initiation of hormone replacement therapy (HRT) at younger ages, use of estrogen-only therapy (ERT), and longer duration of therapy (>5 years) appeared to be associated with lower dementia rates. However, in the meta-analysis, we found no evidence of an overall protective effect of HRT, either for ERT or combined hormone therapy (CHT).

Our systematic review findings are consistent with two recent meta-analyses. Song et al. (2025) reported a protective association when HRT was initiated within five years of menopause (OR 0.70; 95% CI 0.49–0.99) or used for three to five years (OR 0.56; 95% CI 0.34–0.93). Nerattini et al. (2023) analyzed randomized controlled trials (RCTs) and observational studies separately and found an increased risk of Alzheimer's disease (AD) in RCTs, but a reduced risk in observational studies for both AD (RR 0.78; 95% CI 0.64–0.95) and all-cause dementia (RR 0.81; 95% CI 0.70–0.94). In our pooled analysis, the crude model suggested a borderline protective effect (OR 0.83; 95% CI 0.70–0.99) with very high heterogeneity ($I^2 = 99.8\%$). After adjustment, the association was null (OR 0.98; 95% CI 0.89–1.07; $I^2 = 98.1\%$).

The observed heterogeneity likely reflects substantial variation in study design, data sources, and covariate structures. Many datasets were not originally assembled to evaluate HRT–dementia relationships, increasing the potential for residual confounding despite the large cumulative sample size (14,574,096 participants compared with 7,710,379 in Song et al. (2025) and approximately six million in Nerattini et al. (2023)).

In subgroup analyses, ERT demonstrated a non-significant trend toward a protective association (OR 0.77; 95% CI 0.59–1.01; $I^2 = 98.9\%$), whereas CHT did not (OR 0.94; 95% CI 0.64–1.37; $I^2 = 99.7\%$). Despite the high heterogeneity, multiple studies support a timing effect, whereby initiation within ten years of menopause is associated with lower dementia or AD risk, while later initiation confers no apparent benefit. This pattern aligns with the critical-window hypothesis, suggesting that early postmenopausal therapy may preserve neuronal and vascular integrity. The apparent effect of HRT on AD risk may also have attenuated over recent decades, potentially reflecting

Author and Year	Nationality	Baseline age of hormone initiation (Mean(SD)/Median[IQR])	Inclusion criteria	Study design	Sample size	Follow-up (Mean (SD) / Total)	Exposure	Covariates adjusted for	Method of collection or definition of exposure	Outcome	Method of collection or definition of outcome	Outcome measure
Shumaker, et al. 2003	USA	70.6 (5.8)	1) Postmenopausal women 65–79 years in WHI with uterus 2) No dementia at baseline	RCT	4532	Mean: 4.05 (1.19) Total: 8	Oral CEE 0.625 mg/d + MPA 2.5 mg/d Versus placebo	Primary HRs are unadjusted Cox; exploratory models adjust only for one covariate at a time along with treatment.	NA	AzD	Probable Dementia: DSM-IV criteria met after staged cognitive/neuropsych testing, full medical/neuroimaging workup (to exclude reversible causes), and final blinded central adjudication. MCI: Cognitive performance ≤10th percentile on ≥1 CERAD test, mild functional impairment that does not interfere with basic ADLs, and no dementia adjudication.	HR
Shumaker, et al. 2004	USA	70.6 (5.8)	1) Postmenopausal women 65-79 years in WHI with prior hysterectomy 2) No baseline dementia	RCT	2947	Mean: 5.21 (1.73) Total: 10	Oral CEE 0.625 mg/d Versus placebo	Primary HRs are unadjusted Cox; exploratory models adjust only for one covariate at a time along with treatment.	NA	AzD	Probable Dementia: DSM-IV criteria met after staged cognitive/neuropsych testing, full medical/neuroimaging workup (to exclude reversible causes), and final blinded central adjudication. MCI: Cognitive performance ≤10th percentile on ≥1 CERAD test, mild functional impairment that does not interfere with basic ADLs, and no dementia adjudication.	HR
Tang, et al. 1996	USA	74.2 (7.0)	Elderly women from a community study on aging in northern Manhattan, New York City, who had no cognitive impairment, no stroke, no Parkinson's disease, had data on postmenopausal estrogen use, and completed at least one follow-up visit.	Prospective cohort	1124	Range 1-5	Oral CEE Mean duration: 6.8 years	Age, education; ethnic origin; APOE genotype, Participation group (senior centre/housing vs Medicare sample).	Self-reported postmenopausal oral estrogen use, collected at baseline interview via a standardized, interviewer-administered questionnaire.	AzD	Annual clinical + neuropsychological assessments; dementia diagnosis required objective cognitive decline plus functional impairment; Alzheimer's etiology assigned using standard NINCDS-ADRDA criteria by a blinded consensus panel using records, imaging, and exams.	RR
Kawas, et al. 1997	USA	61.5 (16.5)	1) Post or peri-menopausal women. 2) Participants on the BLSA/NIA study. 3) Follow up for 16 years in BLSA/NIA	Retrospective cohort	514	Total: 16	Oral or transdermal ERT	Age; education; NSAID use; estrogen exposure (time-dependent ERT use variable).	Exposure was prospectively ascertained at each scheduled BLSA visit by direct report of medication use (including estrogen) during a standardized medical history/medication review.	AzD	Dementia diagnosis required neurologic exam plus labs/imaging; AD cases had to satisfy DSM-III-R criteria for dementia and NINCDS-ADRDA criteria for definite/probable/possible AD.	RR
Baldereschi, et al. 1998	Italy	ERT never users: 74.7 (5.8); ERT ever users: 73.2 (5.4)	1) Postmenopausal women aged 65 to 84 years 2) Both free dwelling and institutionalized, selected from the population registers of eight Italian municipalities.	Retrospective cohort	1568	NR	ERT Mean duration: 3.1 (4.3)	Age, education, age at menarche, age at menopause, smoking habits, alcohol consumption, body weight at age 50, number of children.	A standard history of ERT use was obtained by directly interrogating each participant and by interrogating the proxy respondent for those who screened positive for dementia.	AzD	All women were screened using the MMSE. Those who screened positive underwent a clinical assessment. Alzheimer's disease was diagnosed according to NINCDS-ADRDA criteria for possible and probable Alzheimer's disease.	OR
Mitchell, et al. 2003	USA	70.1 (NR)	1) Postmenopausal women who participated in the 5 year follow-up examination for the Epidemiology of Hearing Loss Study, 2) Residency at Beaver Dam, Wis from 1987-1988, 3) Participation in the Beaver Dam Eye Study, 4) Being alive by march 1 1993	Prospective cohort	1462	Total: 10	Mostly oral ERT and CRT Mean duration: 3.4 years	Age and education.	Questionnaire + pill-bottle/product inventory; duration computed across visits	AzD	Outcome definition: Abbrev/full MMSE cut-points (≤17/21 or ≤24/30) or AD by self-report.	OR
Petitti, et al. 2007	USA	78.7 (3.2)	1) Postmenopausal women aged 75 years or more.	Prospective cohort	2906	Total: 5	Oral CEE and CEE + MPA Mean duration: 30.5 and 23.2 years	Age, education, myocardial infarction, stroke, Parkinson's disease, diabetes, hypertension.	Pharmacy data (primary) + self-report (initiation/menopause timing).	AzD and AzD	Annual telephone-based multistage ascertainment (TICSm → TDQ proxy → medical records), blinded to HT; operational dementia definition stricter than DSM-IV; validated with high specificity.	HR
Ryan, et al. 2009	France	HRT never users: 74.9 (5.3); HRT past users: 72.4 (4.7); HRT current users: 70.2 (3.3)	1) Postmenopausal women aged 65 or more 2) From the cities of Montpellier, Bordeaux and Dijon 3) Non-institutionalized	Prospective cohort	3130	Total: 4	Oral and transdermal ERT, CRT, PRT	Age; education; study center; marital status; caffeine; BMI; age at menopause; anticholinergic meds; depressive symptoms; comorbidity; physical incapacities; APOE e4; and (for longitudinal cognitive change) baseline cognitive score. Cox dementia models used age as the time scale.	Questionnaire + verification (pill/prescription check) for current HT; detailed history for past use/duration/timing; menopause characteristics recorded.	AzD and AzD	Standardized neurocognitive battery with quintile-based thresholds; DSM-IV dementia, panel-validated.	OR and HR
Whitmer, et al. 2011	USA	48.7 (NR)	Women aged 40–55 who took part in routine health checkups in San Francisco and Oakland, California (1964–1973), were postmenopausal at the exam, alive and health plan members in 1994, and had no dementia before 1999.	Retrospective cohort	5504	Total: 9	Oral or transdermal CEE or CEE + MPA	Age (time scale); education; race; BMI; parity (number of children); diabetes; hypertension; hyperlipidemia; stroke. (+ hysterectomy in sensitivity).	Midlife exposure: self-report at standardized midlife exam. Late-life exposure: objective pharmacy fills (1994–1998) defining users vs nonusers.	AzD	Registry-based diagnosis codes (outpatient/inpatient) for AD/vascular/unspecified dementia	HR
Shao, et al. 2012	USA	HRT never users: 76.7 (6.9); HRT ever users: 73.4 (5.6)	1) Postmenopausal women aged 65 years or older 2) No dementia at baseline	Prospective cohort	1768	Mean: 7 (NR) Total: 12	Oral, cream or transdermal ERT or CRT	Age, APOE e4, education, and an HT-use propensity score summarizing many AD and HT-related risk factors.	Structured telephone WHQ interview in early follow-up	AzD and AzD	Standardized in-person cognitive screening → neuropsychological and clinical workup → blinded expert consensus using DSM-III-R and NINCDS-ADRDA diagnostic criteria, plus MRI and labs when indicated.	HR
Bove, et al. 2014	USA	78 (NR). Range: 53-100)	1) Female, enrolled in ROS or MAP 2) Cognitively non-demented at baseline 3) Available reproductive history (age at menarche, menopause, HRT) 4) Consented to annual follow-up and brain donation	Prospective cohort	1884	Total: 18	Oral HRT	Age, education, smoking, and study (ROS vs MAP).	Exposure data come from structured baseline interviews plus medication verification, not billing codes or pharmacy databases.	AzD	Outcomes are objectively measured annually (cognition and NINCDS-ADRDA), adjudicated clinically (incident AD), and confirmed pathologically at autopsy.	OR and HR
Imtiaz, et al. 2017a	Finland	NR	1) Female gender Resident of Finland on December 31, 2005	Prospective cohort	338086	Total: 10	Systemic therapy HRT	Age; BMI; alcohol; smoking; physical activity; occupation status; number of births; menopause status; any cancer; and surgery (hysterectomy/oophorectomy). Education included only in sensitivity subset.	Self-administered postal questionnaires at baseline and at 5-, 10-, 15-, 20-year follow-ups; plus national prescription register data from 1995 onward.	AzD and AzD	Incident, clinically verified Alzheimer's disease (and, in sensitivity activity; occupation status; number of analyses, any dementia). AD diagnoses were identified in the births; menopause status; any cancer; national special reimbursement register (1999–2009) and must satisfy DSM-IV and NINCDS-ADRDA criteria, supported by neuroimaging/CSF and confirmed by a neurologist/geriatrician for reimbursement.	HR
Song, et al. 2020	Singapore	53.4 (6.4)	1) Patient that were followed for 3 visits 2) That were alive for this trial, and 3) Were contacted by the researcher's group. 4) Natural menopause	Prospective cohort	8222	Range: 16-23	HRT	Age at SM-MMSE measurement, year of baseline interview, dialect group, marital status, education level, smoking, tea intake, coffee intake, sleep duration, physical activity, BMI, total energy intake, alternate Mediterranean diet score, parity (number of children), oral contraceptive use, plus manual adjustment among age at menarche, age at menopause, and HRT use.	Interviewer-administered structured questionnaires.	AzD	Trained interviewers administered the Singapore Modified Mini-Mental State Examination in-home at follow-up 3; cognitive impairment was defined based on SM-MMSE cutoff scores.	OR
Kim, et al. 2021	USA	HRT never users: 67.5 (3.7); HRT ever users: 68 (3.9)	Women aged 45 or older from the Humana insurance database in Louisville, Kentucky (2007–2016), who had at least 6 months of medical and pharmacy coverage before and 2 years after the index date.	Retrospective cohort	1211215	Mean: 5.1 (2.3)	Oral, transdermal or injection HRT	Age, race, region, Charlson Comorbidity Index, individual comorbidities (CVD, T2DM, hypertension, stroke, CKD, COPD), and calendar year of first record.	Hormone use was identified through prescription claims data from the Humana insurance database using Drug Codes and National Drug Codes (NDCs).	AzD	ICD-9-CM and ICD-10-CM diagnosis codes.	RR
Kim, et al. 2022	Korea	NR	1) Female subjects aged 40 years or older; 2) Postmenopausal women; 3) Previous diagnosis of depression	Retrospective cohort	209588	Mean: 7.72 (1.87) Total: 8	Oral Contraceptive (OC), HRT	Age, BMI, level of income, current smoking, drinking status, regular exercise, diabetes mellitus, hypertension, and dyslipidemia.	Self-administered national screening questionnaires at baseline asked about lifetime OC use and HRT use (including duration).	AzD	New diagnosis code for dementia subtype (ICD-10: F900 and F30 for AD; F01 for VD; and F02, F03, and F51 for other dementia") AND at least one prescription of a dementia medication (donepezil, rivastigmine, galantamine, or memantine), during follow-up.	HR
Sung, et al. 2022	Taiwan	NR	Women aged 40 or older from Taiwan's LHID 2000 database who were premenopausal or postmenopausal between 2000 and 2005. The exposed group filled at least two HRT prescriptions after the index date, while the comparison group had no HRT prescriptions during the study period.	Retrospective cohort	105072	Mean: 12.3 (2.3)	Oral, transdermal or injection HRT, Selective estrogen receptor modulators (SERMs)	Age, Age at menopause, index date, hypertension, diabetes, hyperlipidemia, CAD, stroke, COPD, CKD, malignant neoplasms, CCI.	Documented HRT prescriptions in the Taiwanese National Health Insurance claims database.	AzD and AzD	Diagnosis of dementia recorded in claims (ICD-9-CM), confirmed by specialists, plus dementia-specific medication use, and only counted if it occurred ≥1 year after index date.	HR
Yuk, et al. 2023	Korea	58.0. Range: 52-64	1) Women >40 years-old 2) Menopause after 2002. 3) At least 1 MHT prescribed within 2002-2011	Retrospective cohort	1399256	Median: 11.5-14.2 depending on exposure group.	Oral or transdermal Tibolone, CRT, ERT Median duration: 25 months (range: 10–55 months)	Age group, age at menarche, age at menopause, BMI, socioeconomic status, region (urban/rural), Charlson Comorbidity Index, parity, period from menopause to inclusion, smoking status, alcohol consumption status, and physical exercise.	Korean National Health Insurance Service (NHIS) claims database.	AzD and AzD	Dementia defined using ICD-10 codes: AD dementia (F00 or G30); non-AD dementia (F01, F02, F03, G23.1, or G31). A case required visits to ≥3 medical institutions.	HR
Liao, et al. 2023	England, Scotland, and Wales	Age at menopause: ≥50: 60.7 (4.7); 40-49: 59.0 (6.3); <40: 58.8 (7.2)	1) Women from the UK Biobank cohort, postmenopausal, aged 37–73 years, 2) Complete information on age at menopause, no prior diagnosis of dementia at baseline	Prospective cohort	154549	Median: 12.3	HRT	Age at baseline, ethnicity, education, socioeconomic deprivation (SED), smoking status, alcohol intake, low physical activity, healthy diet.	HRT exposure from self-report plus drug-coded medication data collected during verbal interview/medication codes.	AzD	Dementia identified via UK Biobank algorithm using EHR ICD-9 and ICD-10 codes; incident dementia date =. First recorded dementia code; censoring at dementia, death, or June 30, 2021.	HR
Baik, et al. 2024	USA	HRT never users: 65.2 [2]; HRT ever users: 63.1 [1.8]	1) Women entitled to medicare, 2) 65 years or older (+1month), 3) Full lenght of medicare part D benefits (14 years), 4) At least 6 months of data, 5) Indication of HT being menopausal symptoms	Retrospective cohort	10944328	Median: 4.1 Total: 14	HRT	Age, race, income proxy, rural residence, calendar year of Part D enrollment, and 49 CMS Chronic Condition Warehouse chronic conditions (>1% prevalence), all treated as time-varying except race; plus two time-varying propensity scores (probability of HT use and probability of censoring due to plan change/dropout).	Medicare Part D prescription claims.	AzD	Medicare encounter claims (Parts A/B/C) and vital status.	HR

Table 1: *Characteristics of included studies.*

Huh, et al. 2024	Korea	66.0 (8.7)	1) Women who reported menopause at >40 years old using de National Cancer Screening Program Questionnaire. 2) Diagnosis of CKD between 2009 and 2013	Retrospective cohort	9379819	Median: 7.3 [IQR 5.8-8.7]	HRT	Age, BMI, income level, smoking, drinking, diabetes, hypertension, dyslipidemia, physical activity, age at menarche, age at menopause, oral contraceptive use, parity, breastfeeding duration.	Self-reported in a standardized national screening questionnaire.	AcD and AzD	Dementia outcomes were defined using ICD-10 diagnostic codes plus evidence of prescriptions for dementia-related drugs.	HR
Paganini-Hill, et al. 1996	USA	NR	1) Residents of the Leisure World Laguna Hills retirement community, who replied to a health survey questionnaire sent from 1981 until 1985. 2) Female cohort members who had Alzheimer's Disease or any other dementia ascertained in their death certificate.	Case-Control	1446	Mean: 9.2 (NR)	All routes CEE	Estrogen use, age at menarche, weight, type of menopause (natural vs surgical), age at last menstrual period, and use of blood pressure medication.	Self-reported periodical surveys.	AzD	Outcome status was determined by review of official death certificates for all deceased cohort members, supplemented by routine surveillance to ensure capture of deaths; diagnoses consistent with Alzheimer disease were coded as cases.	OR
Costa, et al. 1999	USA	ERT never users: 72.6 (9.5); ERT ever users: 68.9 (9.6)	Postmenopausal women identified from the 1988 baseline dataset, matched with one-year follow-up data, who were outpatients at California State ADDTC, referred for memory problems, assessed with ADDTC-MUDS and BRDRS, and had documented ERT use at both time points.	Case-Control	3128	Total: 1	ERT	BRDRS score (baseline cognitive impairment), age, education, and duration of dementia symptoms (years symptomatic).	Clinic records within the statewide Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) dataset.	AzD	Diagnostic classification (possible/probable SDAT, cognitive impairment, no dementia) followed standardized clinical criteria (NINCDS-ADRDA).	No HR, RR or OR
Waring, et al. 1999	USA	NR	1) Cases: Postmenopausal women diagnosed with AzD between 1980 and 1984. 2) Controls: Postmenopausal women without dementia, matched to cases by age (±3 years) and duration of medical record availability.	Case-Control	444	Median: 5 Total: 6	Oral CEE 0.625mg/d Duration: More than 6 months	Age, education, and type of menopause (surgical vs. natural), along with comorbidities such as hypertension, stroke, and diabetes.	Medical record abstraction through the Rochester Epidemiology Project; prescriptions and pharmacy data were reviewed to confirm ERT use.	AzD	Case identification from medical records and death certificates, using DSM-III and NINCDS–ADRDA criteria for probable/possible Alzheimer's disease.	OR
Seshadri, et al. 2001	United Kingdom	NR	Women born on or before January 1, 1950, in the UK General Practice Research Database, with a first diagnosis of Alzheimer's, senile, or presenile dementia between 1992 and 1998, selected from ERT user and nonuser cohorts without prior knowledge of ERT use.	Case-Control	221406	Mean: 5.34 Range 2.04-7.79+HZ7	Oral or transdermal ERT or CRT Duration: more than 12 months	BMI and cigarette smoking. Sensitivity models: additional cardiovascular/metabolic factors (hypercholesterolemia, diabetes mellitus, ischemic heart disease).	UK General Practice Research Database (GPRD) via computerized prescription records.	AzD	AD cases were identified through the GPRD diagnostic codes, then validated by blinded neurologist review using NINCDS-ADRDA criteria for probable/possible Alzheimer's disease, requiring ≥6 months of progressive cognitive decline in ≥2 domains.	OR
Roberts, et al. 2006	USA	ERT never users: 50.5 [NR]; ERT ever users 49.0 [NR]	Cases were women diagnosed with Alzheimer's disease between 1985 and 1989, meeting DSM-IV criteria, confirmed by a dementia specialist, and with complete medical records. Controls were matched by age and residency, had no dementia in the index year, and also had complete medical records.	Case-Control	528	NR	Oral or parenteral ERT Duration: more than 6 months	Adjusted for age and smoking status.	The Rochester Epidemiology Project records-linkage system. Collected By: A trained nurse abstractor.	AzD	Diagnosis of AD was based on comprehensive medical record review for each subject in the Rochester Epidemiology Project. The diagnosis of dementia and AD followed DSM-IV criteria, confirmed by a dementia specialist (neurologist). Controls were required to have no record of cognitive impairment before the matched "index year."	OR
Imtiaz, et al. 2014	Finland	NR	1) Female gender 2) Resident of Finland on December 31, 2005 3) Clinically verified diagnosis of AzD (per NINCDS-ADRDA and DSM-IV), confirmed by a neurologist or geriatrician 4) Age over 42	Case-Control	38086	Total: 11	Oral or transdermal HRT	Charlson comorbity index, HRT duration, cancer, surgical status (oophorectomy, hysterectomy).	National Hospital Discharge Register procedure codes (1986–2005).	AzD	AD cases were identified from the Finnish Special Reimbursement Register. To qualify in that register, patients must have a clinically verified AD diagnosis made by a geriatrician or neurologist, fulfilling NINCDS-ADRDA and DSM-IV criteria, including progressive cognitive decline plus supportive neuroimaging or CSF biomarkers.	OR
Imtiaz, et al. 2017b	Finland	AD cases, ERT ever users: 64.1. Range: 58.6-69.3 Controls, ERT ever users: 63.8. Range: 58.3-69.1	1) Woman aged 47-56 years in 2) Resident of Kuopio Province, Finland. 3) Who completed the baseline questionnaire and had complete data on confounders and self-reported HT exposure	Case-Control	8195	Total: 16	Oral or transdermal ERT, PRT, CRT	Age, sex, and region-matching, socioeconomic status, comorbidity index, gynecologic surgeries, gynecologic cancer.	National pharmacy dispensing data using ATC codes, modeled into continuous drug-use periods with PREDUP.	AzD	AD cases came from the national Special Reimbursement Register. Diagnosis required: progressive cognitive decline for ≥3 months; impairment consistent with mild/moderate AD; imaging (CT/MRI); exclusion of alternative causes; and confirmation by a neurologist or geriatrician, meeting NINCDS-ADRDA and DSM-IV criteria.	OR
Savolainen-Peltonen, et al. 2019	Finland	AD cases ,ERT ever users: 58.0 (9.3) AD cases, CRT ever users: 56.1 (7.8) Controls, ERT ever users: 57.7 (9.0) Controls, CRT ever users: 55.8 (7.6)	1) Finnish postmenopausal women diagnosed with Alzheimer's diseased between 1999-2013 2) Age and hospital district - matched controls	Case-Control	169478	Cases: 11.4 (8.6) / Controls: 11.5 (8.6)	Oral and transdermal Estradiol, Estradiol + Progestagen or Tibolone	Cases and controls were matched by age and region; No explicit adjustment for other factors like education or APOE status, though these were discussed.	Finnish national drug reimbursement register.	AzD	Clinically and complementary verified Alzheimer's disease diagnosis documented by specialist.	OR
Vinogradova, et al. 2021	United Kingdom	NR	1) Women aged ≥55 2) Registered for ≥10 years in the QResearch or CPRD UK databases 3) With or without a dementia diagnosis between 1998–2020	Case-Control	118501	Cases: 16.0 (4.3) / Controls: 15.8 (4.2)	Oral, subcutaneous or transdermal CEE, Estradiol, Norethisterone, Levonorgestrel, Medroxyprogesterone, Dydrogesterone and Tibolone	Smoking, alcohol use, BMI, ethnicity, socioeconomic deprivation (Townsend fifth in QResearch), family history of dementia, history of oophorectomy/hysterectomy, recorded menopausal symptoms/early menopause, multiple comorbidities (eg, diabetes, hypertension, CHD, stroke, depression), use of other drugs (eg, anticholinergics, antidepressants, antipsychotics), and years of recorded data.	Records in primary care electronic health records (QResearch and CPRD).	AzD	Identified from general practicioners records, hospital episode statistics, and mortality data and/or dementia-specific prescriptions;	OR
Lokkegaard, et al. 2022	Denmark	NR	Singletons were individuals without a twin, born before 1930, alive by 1995, and first diagnosed with dementia after 1997 at age 69 or older. Twins were living co-twins without dementia at the time of their twin's diagnosis, meeting the same criteria as singletons.	Case-Control	13263	Before 2003 (1995-2011): Total 17 After 2003 (2005-2011): Total 15	Oral or transdermal HRT	Age and education.	Danish National Prescription Registry	AcD	First hospital diagnosis of dementia, collected from the Danish National Registry of Patients.	OR
Pourhadi, et al. 2023	Denmark	AD cases, CRT ever users: 53 (50-54) Controls, CRT ever users: 53 (50-54)	Women aged 55–60 on January 1, 2000, from Danish National Registries, with records of menopausal hormone therapy prescriptions, no history of thrombotic events or cancer, and no prior dementia for controls.	Case-Control	61479	Total 19	Oral or transdermal / Continuous or cyclical Estradiol + Norethisterone; Estradiol + Medroxyprogesterone; Estradiol + Levonorgestrel; Estradiol + Cyproterone; Estradiol + Dienogest	Age, education, income, cohabitation, hypertension, diabetes, and thyroid disease.	Danish National Prescription Registry	AcD	First-time diagnosis of all-cause dementia or prescription redemption of antidementia medication from the National Registry of Patients.	OR
Pourhadi, et al. 2024	Denmark	AD cases, ERT ever users: 53 (51-54) Controls, ERT ever users: 53 (51-54)	1) Women with hysterectomy, 2) Ages 50 to 60 years, 3) No previous dementia.	Case-Control	29104	Total 19 Total (cases): 15 [IQR 11-17], Total (controls): 19 [IQR 19-19]	Oral or transdermal Estradiol <2mg, 2-<3 mg and ≥3mg Median daily oral dose: 2 mg (IQR 1.9–2.0) Median daily transdermal dose: 0.07 mg/d (IQR reported) Duration (median): 5.4 (cases) and 5.1 (controls)	Age, education, income, cohabitation, hypertension, diabetes, thyroid disease at index date.	Danish National Prescription Registry	AcD	First-time diagnosis of all-cause dementia or prescription redemption of antidementia medication.	OR

Table 1: *(continued) Characteristics of included studies.*

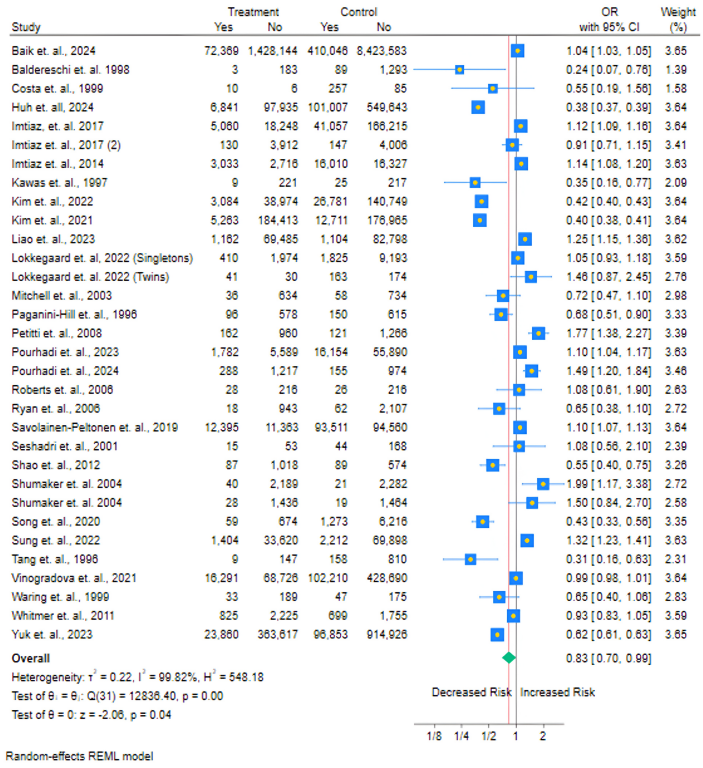

Figure 2: *Forest plot of unadjusted effect estimates for hormone replacement therapy (HRT) and dementia risk.*

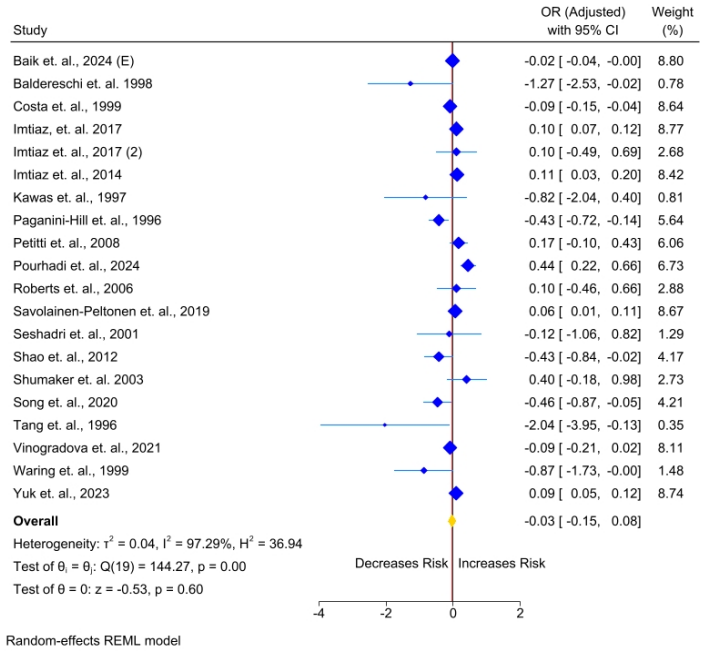

Figure 3: *Forest plot of adjusted effect estimates for estrogen replacement therapy (ERT) and risk of dementia.*

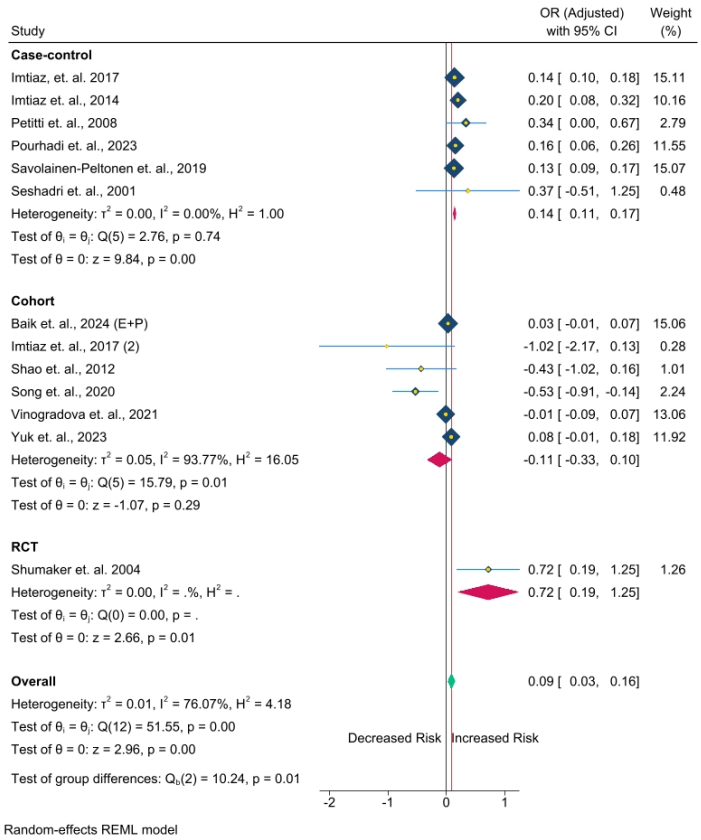

Figure 4: *Forest plot of adjusted effect estimates for combined hormone therapy (CHT) and risk of dementia.*

improvements in cardiovascular and metabolic risk-factor management.

Sources of heterogeneity across studies were diverse and included differences in age distributions, hormone formulations, dosages, and routes of administration. Sensitivity analyses indicated that a single study (Kim et al., 2021) contributed the greatest statistical weight to the pooled estimates.

Most included studies were observational, contributing to an elevated risk of bias. Many lacked adequate covariate adjustment or employed heterogeneous diagnostic criteria. Education, cardiovascular health, and healthcare-seeking behaviors are plausible confounders. Effect estimates varied by study design, with cohort studies appearing more sensitive to HRT exposure than case–control or experimental designs. Although RCTs offer stronger control of confounding, dementia's long latency, limited follow-up duration, and variable outcome ascertainment constrain inference. For example, the Women's Health Initiative Memory Study (WHIMS) (Shumaker et al., 2003; Shumaker et al., 2004) had a five-year follow-up with incomplete dementia ascertainment; in our analyses, RCTs tended to show increased risk but did not materially alter overall or sensitivity results.

HRT type was reported in two RCTs, sixteen cohort studies, and twelve case–control studies. The high heterogeneity likely reflects differences in population composition, timing of initiation, hormone regimens (dose, route, formulation), and diagnostic criteria. Overall, our synthesis suggests that ERT may be associated with lower AD risk compared with no therapy, whereas progesterone-containing regimens do not demonstrate a clear benefit.

Clinically, these findings underscore the potential importance of early initiation and therapy type. Strengths of our study include the large pooled sample size and prespecified subgroup analyses by HRT type. Limitations include substantial heterogeneity, variability in study design, and incomplete reporting of follow-up duration. External validity is also limited, as most studies were conducted in high-income settings using heterogeneous methodologies. Two studies contributed disproportionately to concerns regarding risk of bias. Baldereschi et al. (1998) included a cross-sectional component despite longitudinal follow-up interviews, limiting temporal inference, while Song et al. (2020) assessed cognitive impairment rather than clinically confirmed dementia, introducing outcome heterogeneity and reducing comparability across studies.

Conclusion

In conclusion, the association between HRT and cognitive outcomes remains controversial. While our systematic review suggests a possible protective association for estrogen-only therapy, our meta-analysis did not confirm an overall protective effect. Timing, duration, and regimen likely modify dementia risk among postmenopausal women. Future research should prioritize well-designed RCTs with sufficient power, long-term follow-up, harmonized diagnostic criteria, and prespecified subgroup analyses. Rigorous control of genetic, cardiovascular, social, and lifestyle confounders will be essential to clarify the true effect of HRT on dementia risk.

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Supplementary Materials

Search strategy, risk of bias assessments and additional forest plots from sensitivity and subgroup analyses.

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Conflicts of Interest

The authors declare no conflict of interest.

References

Baik, S. H., Baye, F., & McDonald, C. J. (2024). Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses. Menopause, 31(5), 363–371. https://doi.org/10.1097/GME.0000000000002335

Baldereschi, M., Di Carlo, A., Lepore, V., Bracco, L., Maggi, S., Grigoletto, F., Scarlato, G., & Amaducci, L. (1998). Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. Neurology, 50(4), 996–1002. https://doi.org/10.1212/WNL.50.4.996

Bove, R., Secor, E., Chibnik, L. B., Barnes, L. L., Schneider, J. A., Bennett, D. A., & De Jager, P. L. (2014). Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology, 82(3), 222–229. https://doi.org/10.1212/WNL.0000000000000033

Costa, M. M., Reus, V. I., Wolkowitz, O. M., Manfredi, F., & Lieberman, M. (1999). Estrogen replacement therapy and cognitive decline in memory-impaired post-menopausal women. Biological Psychiatry, 46(2), 182–188. https://doi.org/10.1016/S0006-3223(98)00355-2

Gong, J., Harris, K., Lipnicki, D. M., Castro-Costa, E., Lima-Costa, M. F., Diniz, B. S., Xiao, S., Lipton, R. B., Katz, M. J., Wang, C., Preux, P. M., Guerchet, M., Gbessemehlan, A., Ritchie, K., Ancelin, M. L., Skoog, I., Najar, J., Sterner, T. R., Scarmeas, N., Yannakoulia, M., … Cohort Studies of Memory in an International Consortium (COSMIC). (2023). Sex differences in dementia risk and risk factors: Individual-participant data analysis using 21 cohorts across six continents from the COSMIC consortium. Alzheimer's & Dementia, 19(8), 3365–3378. https://doi.org/10.1002/alz.12962

Gu, Y., Han, F., Xue, M., Wang, M., & Huang, Y. (2024). The benefits and risks of menopause hormone therapy for the cardiovascular system in postmenopausal women: A systematic review and meta-analysis. BMC Women's Health, 24(1), 60. https://doi.org/10.1186/s12905-023-02788-0

Huh, H., Kim, M., Jung, S., Cho, J. M., Kim, S. G., Park, S., Lee, S., Kang, E., Kim, Y., Kim, D. K., Joo, K. W., Han, K., & Cho, S. (2024). Menopausal hormone therapy and risk for dementia in women with CKD: A nationwide observational cohort study. Nephrology, 29(3), 126–134. https://doi.org/10.1111/nep.14260

Imtiaz, B., Tuppurainen, M., Rikkonen, T., Kivipelto, M., Soininen, H., Kröger, H., & Tolppanen, A.-M. (2017a). Postmenopausal hormone therapy and Alzheimer disease: A prospective cohort study. Neurology, 88(11), 1062–1068. https://doi.org/10.1212/WNL.0000000000003696

Imtiaz, B., Taipale, H., Tanskanen, A., Tiihonen, M., Kivipelto, M., Heikkinen, A.-M., Tiihonen, J., Soininen, H., Hartikainen, S., & Tolppanen, A.-M. (2017b). Risk of Alzheimer's disease among users of postmenopausal hormone therapy: A nationwide case-control study. Maturitas, 98, 7–13. https://doi.org/10.1016/j.maturitas.2017.01.002

Imtiaz, B., Tuppurainen, M., Tiihonen, M., Kivipelto, M., Soininen, H., Hartikainen, S., & Tolppanen, A.-M. (2014). Oophorectomy, hysterectomy, and risk of Alzheimer's disease: A nationwide case-control

study. Journal of Alzheimer's Disease, 42(2), 575–581. https://doi.org/10.3233/JAD-140336

Johansson, T., Karlsson, T., Bliuc, D., Schmitz, D., Ek, W. E., Skalkidou, A., Center, J. R., & Johansson, Å. (2024). Contemporary menopausal hormone therapy and risk of cardiovascular disease: Swedish nationwide register based emulated target trial. BMJ, 387, e078784. https://doi.org/10.1136/bmj-2023-078784

Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., Bacal, C., Lingle, D. D., & Metter, E. (1997). A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: The Baltimore Longitudinal Study of Aging. Neurology, 48(6), 1517–1521. https://doi.org/10.1212/WNL.48.6.1517

Kim, H., Yoo, J., Han, K., Lee, D.-Y., Fava, M., Mischoulon, D., & Jeon, H. J. (2022). Hormone therapy and the decreased risk of dementia in women with depression: A population-based cohort study. Alzheimer's Research & Therapy, 14(1), 83. https://doi.org/10.1186/s13195-022-01026-3

Kim, Y. J., Soto, M., Branigan, G. L., Rodgers, K., & Brinton, R. D. (2021). Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy. Alzheimer's & Dementia (New York, N. Y.), 7(1), e12174. https://doi.org/10.1002/trc2.12174

Liao, H., Cheng, J., Pan, D., Deng, Z., Liu, Y., Jiang, J., Cai, J., He, B., Lei, M., Li, H., Li, Y., Xu, Y., & Tang, Y. (2023). Association of earlier age at menopause with risk of incident dementia, brain structural indices and the potential mediators: A prospective community-based cohort study. EClinicalMedicine, 60, 102033. https://doi.org/10.1016/j.eclinm.2023.102033

Lin, C.-Y., Zhai, Y.-J., An, H.-H., Wu, F., Qiu, H.-N., Li, J.-B., & Lin, J.-N. (2025). Global trends in prevalence, disability adjusted life years, and risk factors for early onset dementia from 1990 to 2021. Scientific Reports, 15(1), 13488. https://doi.org/10.1038/s41598-025-97404-6

Løkkegaard, L. E., Thinggaard, M., Nygaard, M., Hallas, J., Osler, M., & Christensen, K. (2022). Systemic hormone therapy and dementia: A nested case-control and co-twin control study. Maturitas, 165, 113–119. https://doi.org/10.1016/j.maturitas.2022.04.007

Low, L. F., & Anstey, K. J. (2006). Hormone replacement therapy and cognitive performance in postmenopausal women—a review by cognitive domain. Neuroscience and Biobehavioral Reviews, 30(1), 66–84. https://doi.org/10.1016/j.neubiorev.2005.05.003

Manson, J. E., Chlebowski, R. T., Stefanick, M. L., Aragaki, A. K., Rossouw, J. E., Prentice, R. L., Anderson, G., Howard, B. V., Thomson, C. A., LaCroix, A. Z., Wactawski-Wende, J., Jackson, R. D., Limacher, M., Margolis, K. L., Wassertheil-Smoller, S., Beresford, S. A., Cauley, J. A., Eaton, C. B., Gass, M., … Wallace, R. B. (2013). Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA, 310(13), 1353–1368. https://doi.org/10.1001/jama.2013.278040

Mitchell, J. L., Cruickshanks, K. J., Klein, B. E. K., Palta, M., & Nondahl, D. M. (2003). Postmenopausal hormone therapy and its association with cognitive impairment. Archives of Internal Medicine, 163(20), 2485–2490. https://doi.org/10.1001/archinte.163.20.2485

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine, 6(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Nerattini, M., Jett, S., Andy, C., Carlton, C., Zarate, C., Boneu, C., Battista, M., Pahlajani, S., Loeb-Zeitlin, S., Havryulik, Y., Williams, S., Christos, P., Fink, M., Brinton, R. D., & Mosconi, L. (2023). Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. Frontiers in Aging Neuroscience, 15, 1260427. https://doi.org/10.3389/fnagi.2023.1260427

Neu, S. C., Pa, J., Kukull, W., Beekly, D., Kuzma, A., Gangadharan, P., Wang, L.-S., Romero, K., Arneric, S. P., Redolfi, A., Orlandi, D., Frisoni, G. B., Au, R., Devine, S., Auerbach, S., Espinosa, A., Boada, M., Ruiz, A., Johnson, S. C., … Toga, A. W. (2017). Apolipoprotein E genotype and sex risk factors for Alzheimer disease: A meta-analysis. JAMA Neurology, 74(10), 1178–1189. https://doi.org/10.1001/jamaneurol.2017.2188

Paganini-Hill, A., & Henderson, V. W. (1996). Estrogen replacement therapy and risk of Alzheimer disease. Archives of Internal Medicine, 156(19), 2213–2217. https://doi.org/10.1001/archinte.156.19.2213

Petitti, D. B., Crooks, V. C., Chiu, V., Buckwalter, J. G., & Chui, H. C. (2008). Incidence of dementia in long-term hormone users. American Journal of Epidemiology, 167(6), 692–700. https://doi.org/10.1093/aje/kwm362

Pourhadi, N., Mørch, L. S., Holm, E. A., Torp-Pedersen, C., & Meaidi, A. (2023). Menopausal hormone therapy and dementia: Nationwide, nested case-control study. BMJ, 381, e072770. https://doi.org/10.1136/bmj-2022-072770

Pourhadi, N., Mørch, L. S., Holm, E. A., Torp-Pedersen, C., & Meaidi, A. (2024). Dementia in women using estrogen-only therapy. JAMA, 331(2), 160–162. https://doi.org/10.1001/jama.2023.23784

Roberts, R. O., Cha, R. H., Knopman, D. S., Petersen, R. C., & Rocca, W. A. (2006). Postmenopausal estrogen therapy and Alzheimer disease: Overall negative findings. Alzheimer Disease and Associated Disorders, 20(3), 141–146. https://doi.org/10.1097/00002093-200607000-00004

Ryan, J., Carrière, I., Scali, J., Dartigues, J. F., Tzourio, C., Poncet, M., Ritchie, K., & Ancelin, M. L. (2009). Characteristics of hormone therapy, cognitive function, and dementia: The prospective 3C Study. Neurology, 73(21), 1729–1737. https://doi.org/10.1212/WNL.0b013e3181c34b0c

Ryan, J., Scali, J., Carrière, I., Amieva, H., Rouaud, O., Berr, C., Ritchie, K., & Ancelin, M.-L. (2014). Impact of a premature menopause on cognitive function in later life. BJOG: An International Journal of Obstetrics and Gynaecology, 121(13), 1729–1739. https://doi.org/10.1111/1471-0528.12828

Saleh, R. N. M., Hornberger, M., Ritchie, C. W., & Minihane, A. M. (2023). Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women. Alzheimer's Research & Therapy, 15(1), 10. https://doi.org/10.1186/s13195-022-01121-5

Savolainen-Peltonen, H., Rahkola-Soisalo, P., Hoti, F., Vattulainen, P., Gissler, M., Ylikorkala, O., & Mikkola, T. S. (2019). Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: Nationwide case-control study. BMJ, 364, l665. https://doi.org/10.1136/bmj.l665

Seshadri, S., Zornberg, G. L., Derby, L. E., Myers, M. W., Jick, H., & Drachman, D. A. (2001). Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Archives of Neurology, 58(3), 435–440. https://doi.org/10.1001/archneur.58.3.435

Shao, H., Breitner, J. C. S., Whitmer, R. A., Wang, J., Hayden, K., Wengreen, H., Corcoran, C., Tschanz, J., Norton, M., Munger, R., Welsh-Bohmer, K., Zandi, P. P., & Cache County Investigators. (2012). Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. Neurology, 79(18), 1846–1852. https://doi.org/10.1212/WNL.0b013e318271f823

Shumaker, S. A., Legault, C., Kuller, L., Rapp, S. R., Thal, L., Lane, D. S., Fillit, H., Stefanick, M. L., Hendrix, S. L., Lewis, C. E., Masaki, K., Coker, L. H., & Women's Health Initiative Memory Study. (2004). Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. JAMA, 291(24), 2947–2958. https://doi.org/10.1001/jama.291.24.2947

Shumaker, S. A., Legault, C., Rapp, S. R., Thal, L., Wallace, R. B., Ockene, J. K., Hendrix, S. L., Jones, B. N., Assaf, A. R., Jackson, R. D., Kotchen, J. M., Wassertheil-Smoller, S., Wactawski-Wende, J., & WHIMS Investigators. (2003). Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA, 289(20), 2651–2662. https://doi.org/10.1001/jama.289.20.2651

Song, Q., Wang, Q., Wu, D., Zhang, Z., Chen, M., Fu, C., Li, M., Wang, X., Zhao, Y., & Zhu, D. (2025). Association between duration, initiation time, routes, and formulations of menopausal hormone therapy use and Alzheimer disease in women: A systematic review and meta-analysis. The Journal of Pharmacology and Experimental Therapeutics, 392(5), 103554. https://doi.org/10.1016/j.jpet.2025.103554

Song, X., Wu, J., Zhou, Y., Feng, L., Yuan, J.-M., Pan, A., & Koh, W. P. (2020). Reproductive and hormonal factors and risk of cognitive impairment among Singapore Chinese women. American Journal of Obstetrics and Gynecology, 223(3), 410.e1–410.e23. https://doi.org/10.1016/j.ajog.2020.02.032

Sung, Y.-F., Tsai, C.-T., Kuo, C.-Y., Lee, J.-T., Chou, C.-H., Chen, Y.-C., Chou, Y.-C., & Sun, C.-A. (2022). Use of hormone replacement therapy and risk of dementia: A nationwide cohort study. Neurology, 99(17), e1835–e1842. https://doi.org/10.1212/WNL.0000000000200960

Tang, M. X., Jacobs, D., Stern, Y., Marder, K., Schofield, P., Gurland, B., Andrews, H., & Mayeux, R. (1996). Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. The Lancet, 348(9025), 429–432. https://doi.org/10.1016/S0140-6736(96)03356-9

Vinogradova, Y., Dening, T., Hippisley-Cox, J., Taylor, L., Moore, M., & Coupland, C. (2021). Use of menopausal hormone therapy and risk of dementia: Nested case-control studies using QResearch and CPRD databases. BMJ, 374, n2182. https://doi.org/10.1136/bmj.n2182

Waring, S. C., Rocca, W. A., Petersen, R. C., O'Brien, P. C., Tangalos, E. G., & Kokmen, E. (1999). Post-menopausal estrogen replacement therapy and risk of AD: A population-based study. Neurology, 52(5), 965–965. https://doi.org/10.1212/WNL.52.5.965

Whitmer, R. A., Quesenberry, C. P., Zhou, J., & Yaffe, K. (2011). Timing of hormone therapy and dementia: The critical window theory re-visited. Annals of Neurology 69(1), 163–169. https://doi.org/10.1002/ana.22239

Yuk, J.-S., Lee, J. S., & Park, J. H. (2023). Menopausal hormone therapy and risk of dementia: Health insurance database in South Korea-based retrospective cohort study. Frontiers in Aging Neuroscience, 15, 1213481. https://doi.org/10.3389/fnagi.2023.1213481