Menopause hormone therapy and risk of mild cognitive impairment or dementia: a systematic review and meta-analysis

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Summary

Background Globally, dementia disproportionately affects women. Changes in circulating sex steroids over the menopause transition might contribute to this sex difference. Menopause hormone therapy (MHT) is recommended by the UK National Institute for Health and Care Excellence to manage menopausal symptoms, but whether MHT use affects dementia risk and how this association might vary by age at menopause is unclear. We aimed to assess whether MHT (*vs* no MHT) affects the risk of mild cognitive impairment or dementia in peri-menopausal or post-menopausal women, including those with premature ovarian insufficiency or early menopause (with normal cognition or mild cognitive impairment), and whether MHT type, duration, or age at initiation influence this risk.

Methods We systematically searched MEDLINE via OVID, Embase via Elsevier, Cochrane via OVID, and PsycINFO via OVID for systematic reviews published between Jan 1, 2000, and Dec 19, 2024. As no existing review met our quality or scope criteria, we proceeded to conduct a systematic review and meta-analysis of primary studies published from Jan 1, 2000, to Oct 20, 2025. Eligible primary studies included randomised controlled trials (RCTs), non-randomised intervention studies, and prospective observational studies examining the association between MHT—including oestrogen-only MHT, combined MHT, testosterone, and tibolone—and incident mild cognitive impairment or dementia. Two reviewers independently screened studies, extracted data, and assessed risk of bias using RoB 2 and ROBINS-E, with certainty of evidence rated using GRADE. Meta-analyses pooled relative risk estimates in a random-effects model. The protocol was preregistered on PROSPERO (CRD42025639384).

Findings Of 5914 records, ten studies (one RCT and nine observational studies) with a total of 1 016 055 participants were included. Certainty of evidence ranged from moderate to very low. No included studies examined testosterone or use in premature ovarian insufficiency. No significant association was found between MHT use and risk of mild cognitive impairment or dementia. Subgroup analyses by timing, duration, and type of MHT showed no significant effects.

Interpretation This review found no evidence that MHT use either increases or decreases the risk of dementia in post-menopausal women. This reinforces current clinical guidance, that MHT prescription should be based on other perceived benefits and risks and not for dementia prevention. High-quality, long-term studies are needed to clarify the role of MHT and dementia risk, particularly regarding formulation, dose, route, timing, and duration of treatment, with a focus on women with premature ovarian insufficiency, early menopause, or mild cognitive impairment.

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Introduction

Dementia disproportionately affects women worldwide, even accounting for longer life expectancy.[1] Changes in circulating concentrations of sex steroids over the menopause transition might trigger vasomotor symptoms, sleep, and mood disturbances. Menopause hormone therapy (MHT) might alleviate these symptoms. However, whether MHT affects cognition in the short term or mild cognitive impairment or dementia risk in the longer term remains uncertain.[2–4] Also, whether age at menopause or initiation of MHT or the type of MHT (combined MHT *vs* oestrogen-only MHT) modify this risk is unclear.[4,5]

Early observational studies suggested MHT might reduce dementia risk, particularly when initiated early and used long-term.[6–11] These findings suggested that timing, duration, and formulations might influence outcomes. Use of MHT in some studies was limited to oestrogen-only MHT as progestin was subsequently added (combined MHT) to mitigate endometrial cancer risk.[12] Currently, around 80% of MHT users take combined preparations since they retain their uterus.[13] Since oestrogen-only MHT and combined formulations have different risk profiles, cognitive effects might also be formulation specific. However, observational studies are limited by confounders, and

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Research in context

Evidence before this study

The use of menopause hormone therapy (MHT) to treat menopausal symptoms in women and the associated effect on cognition and dementia remains an area of public and clinical debate, largely due to potential adverse effects and conflicting evidence. In December, 2024, we conducted an umbrella review to identify recent, high-quality systematic reviews on the association between MHT and risk of mild cognitive impairment or dementia in peri-menopausal or post-menopausal women including those with premature ovarian insufficiency or early menopause, with or without mild cognitive impairment. We searched MEDLINE, Embase, Cochrane, and PsycINFO from January, 2020, to December, 2024, alongside PROSPERO, Open Science Framework, and reference lists of guidelines and high-quality reviews. Existing systematic reviews identified were outdated, narrow in scope, or methodologically weak, leaving uncertainty about the relationship between MHT and mild cognitive impairment or dementia, particularly in under-researched subgroups such as women with premature ovarian insufficiency or early menopause. No existing systematic review met the breadth and methodological rigour required for GRADE methodology. The evidence regarding MHT use and mild cognitive impairment or dementia following premature ovarian insufficiency or early menopause was particularly scant and no existing review evaluated the use of testosterone. Reviews generally relied heavily on low-quality observational studies.

Added value of this study

This review is the most comprehensive and methodologically rigorous synthesis to date of RCT and observational evidence on MHT and mild cognitive impairment or dementia risk, stratified by formulation, age at initiation, and duration of use. By focusing on higher-quality studies, we provide more precise pooled estimates and a transparent assessment of certainty using GRADE. We found that MHT neither increases nor decreases risk of mild cognitive impairment or dementia in post-menopausal women.

Implications of all the available evidence

This rigorous review does not support the use of MHT for dementia prevention following menopause at any age, nor does it indicate any association between MHT and dementia risk. For most regimens and subgroups, certainty is very low, and both important benefits and harm remain possible. Future research should prioritise long-term, high-quality studies that address formulation, dose, route of administration, timing of initiation, and treatment duration, with particular focus on premature ovarian insufficiency, early menopause, women with mild cognitive impairment, and the use of testosterone.

these cognitive effects of MHT were not replicated in randomised controlled trials (RCTs), largely due to healthy user bias.[14]

The only RCT of MHT and dementia (The Women's Health Initiative Memory Study [WHIMS]) reported that combined MHT roughly doubled dementia risk whereas oestrogen-only MHT increased the risk of mild cognitive impairment.[4,5] However, participants were initiating MHT at 65 years or older, which is uncommon in practice. It is not known whether risks are similar in those continuing MHT up to 65 years or older.

The 2024 Lancet Commission on dementia[15] highlights the complex link between menopause, MHT, and dementia risk. Observational studies suggest that early menopause (age 40–44 years) might increase dementia risk[16] but that MHT does not prevent this. Large observational studies suggest combined MHT increases dementia risk, especially with long-term use.[17,18] A meta-analysis of high-quality RCTs found no evidence that oestrogen-only MHT prevents dementia and some evidence that it might increase dementia risk.[19] The Lancet Commission concluded that there is limited evidence supporting MHT for dementia prevention and ongoing uncertainty around causality.[15] Similarly, the 2024 UK National Institute for Health and Care Excellence (NICE) menopause guidelines[20] advise against MHT for dementia prevention and recommend informing women of possible non-cognitive age-related risks such as breast cancer and stroke. NICE also identifies key evidence gaps, especially for early menopause and under-represented groups.

Currently, WHO provides no guidance on MHT and cognitive outcomes, leaving a crucial gap for clinicians and policy makers. Commissioned by the WHO, we assessed whether MHT use in peri-menopausal or post-menopausal women, including those with premature ovarian insufficiency or early menopause, affects the risk of mild cognitive impairment or dementia compared with no MHT. This review will inform the update process of the WHO guidelines on risk reduction of cognitive decline and dementia.

Throughout this Article, dementia refers to clinically diagnosed all-cause dementia (including Alzheimer's disease unless specified). Probable dementia refers to cases initially identified via screening and confirmed through clinical and laboratory assessments.[5]

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted in accordance with chapter 8 of the WHO Handbook for Guideline Development[21] and the PRISMA 2020 guidelines.[22] This study is registered on PROSPERO (CRD42025639384). We systematically searched MEDLINE via OVID, Embase via Elsevier, Cochrane via OVID, and PsycINFO via OVID for systematic reviews published between Jan 1, 2000, and Dec 19, 2024; as none met our quality or scope criteria, we then screened primary studies

published from Jan 1, 2000, to Oct 20, 2025. The search strings were developed by two librarians using relevant terms (appendix pp 4–14). Reference lists and forward citations of included studies were screened. Records were uploaded to COVIDENCE, de-duplicated, and screened by title and abstract. Full texts were assessed against inclusion criteria by two independent reviewers, with disagreements resolved by a third. A list of studies excluded at full-text screening is provided in the appendix (pp 16–28).

Given the scarce RCT evidence available, observational studies were included to provide a more comprehensive assessment of dementia risk. Eligible primary studies included RCTs, non-randomised intervention studies, and prospective observational designs (eg, cohort, nested case–control, quasi-experimental). We included studies involving peri-menopausal or post-menopausal women (with normal cognition or mild cognitive impairment), including those with premature ovarian insufficiency (age <40 years) or early menopause (age 40–44 years) as defined by the 2011 update of the Stages of Reproductive Aging Workshop criteria (STRAW+10), which refined the classification of menopausal stages based on hormonal and menstrual cycle changes.[23] Studies had to report a quantitative association between MHT exposure and incident dementia or mild cognitive impairment, based on clinical diagnosis or health-care records. MHT formulations included oestrogen-only MHT (after hysterectomy) or combined MHT (oestrogen and a progestogen [progestin or progesterone]), bazedoxifene, tibolone, or testosterone. Studies not reporting MHT type separately were excluded. Full inclusion and exclusion criteria are in the appendix (pp 2–3).

Data extraction and management

Two reviewers independently extracted data, with validation by a third reviewer. Discrepancies were resolved by consensus or a fourth reviewer. Study authors were contacted for missing data; studies without available data were excluded. Data extracted included author details, country of study, year of publication, study design, sample size, participant demographics and baseline characteristics, intervention (eg, type, duration, timing, dosage, and route of administration where reported), comparator, outcomes, and available unadjusted and adjusted measures of association (effect estimates: odds ratio [OR], risk ratio [RR], or hazard ratio [HR]) with their reported 95% CIs and covariate adjustments.

Risk-of-bias assessment of included primary studies

Using the Cochrane risk-of-bias tool for randomised trials (RoB 2) or Cochrane risk-of-bias tool for non-randomised studies of exposures (ROBINS-E), risk of bias was assessed by one researcher and independently validated by a second, with discrepancies resolved by consensus. All ratings are summarised in the appendix (p 15).

Data synthesis

Random-effects meta-analyses were conducted using the metafor[24] package in R (version 2025.09.2+418) for subgroups by outcome (eg, dementia or Alzheimer's disease), MHT type (oestrogen-only MHT or combined MHT), duration (short term, medium term, or long term), and age at initiation (45–55 years or ≥60 years). Narrative synthesis was used when meta-analysis was not feasible.

See Online for appendix

To avoid participant overlap, only one estimate per cohort was included in each meta-analytic model, prioritising larger samples and longer follow-up. Where two or more similar estimates were available, data were pooled using a random-effects meta-analysis model employing the inverse variance weighted method to account for expected heterogeneity across populations, interventions, and follow-up durations.

HRs and ORs were converted to RRs using established methods,[25,26] to ensure consistent interpretation across studies. Conversions were guided by an a priori threshold based on baseline incidence: when incidence was below 15%, HRs and ORs were treated as approximate RRs; when above 15%, conversions were applied to reduce bias. Baseline incidence was calculated from control groups or, if unavailable, from the overall study population. For studies with potentially overlapping populations, we ran sensitivity analysis and compared the results with the primary findings.

Assessment of certainty of evidence (GRADE evidence profiles)

We applied the GRADE framework to assess the certainty of evidence as high, moderate, low, or very low. At least two reviewers independently rated the evidence, resolving discrepancies through discussion. Ratings were based on study design, risk of bias, imprecision, inconsistency, and publication bias, with observational studies initially rated as low certainty and RCTs as high. To support interpretation, we applied partially contextualised thresholds: absolute differences greater than 10 per 1000 were considered important, whereas differences of 10 per 1000 or fewer were considered trivial. Baseline risk was calculated using weighted averages from control group incidence across studies contributing to each meta-analytic model.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Across four databases we found a total of 5914 records (figure 1). An additional five records were identified through forward and backward citation searches. We removed 2401 duplicates and screened a total of 3518 records; 167 articles were evaluated in full-text and 15 were included in the review (table 1).[4,5,17,18,27–37] Due to overlapping datasets, the GRADE analysis included only ten studies comprising one RCT[4] and nine observational studies.[4,17,18,27,29–34] Outcomes assessed included incidence of all-cause dementia, Alzheimer's disease, and dementia or mild cognitive impairment. Due to differences in

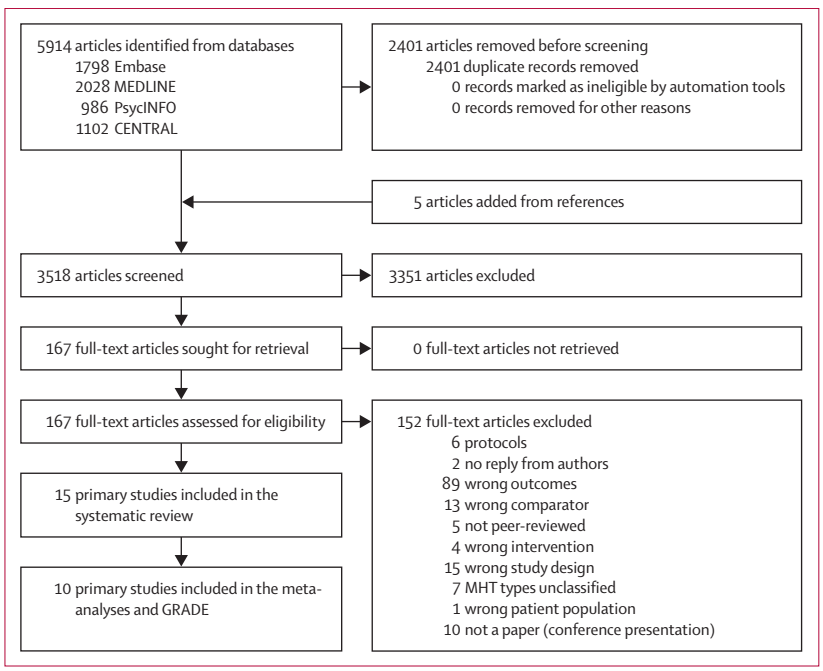


Figure 1: **PRISMA 2020 flow diagram of study selection process**

methodological robustness, studies were grouped and evaluated separately by design (RCT *vs* observational) and further categorised by MHT type, timing, and duration of initiation.

GRADE-rated evidence on the associations between MHT type, timing, and dementia outcomes of observational evidence was judged as very low certainty, whereas the single included RCT provided moderate certainty in one analysis and low in another due to wide confidence intervals (table 2; appendix pp 29–59). A visual summary of GRADED evidence (adapted from Negrini and colleagues)[38] is shown in the appendix (p 60).

For oestrogen-only MHT versus no MHT with outcome (all-cause) dementia, evidence from the WHIMS RCT[4] (n=1464; follow-up 5·21 years) suggests oestrogen-only MHT might increase dementia risk in women aged 65 years or older (HR 1·49 [95% CI 0·83–2·66]), but certainty is low due to serious imprecision. The absolute risk difference was 6·27 additional cases per 1000 women, indicating little to no difference in dementia risk when initiated after age 65 years.

A meta-analysis of five observational studies[17,30–33] (n=672 195; follow-up 3·4–19·0 years) found a pooled RR of 1·10 (95% CI 0·93–1·31; I^2=81·41%) for oestrogen-only MHT and dementia risk, suggesting a possible slight increase in risk (figure 2A). Certainty was very low due to bias, inconsistency, imprecision, and indirectness. The confidence interval includes both potential benefit and harm and the absolute effect was below our threshold for clinical importance, leaving the effect uncertain. The sensitivity analysis excluding Pourhadi and colleagues[32] due to potentially overlapping controls with their 2024 study[33] yielded consistent results with a pooled RR of 1·12 (95% 0·89–1·41; I^2=81·36%).

For oestrogen-only MHT versus no MHT with outcome Alzheimer's disease, a meta-analysis of four large observational studies[17,29,32,34] (n=874 102; follow-up 6–19 years) found a pooled RR of 0·95 (95% CI 0·82–1·11; I^2=77·13%), suggesting a possible small risk reduction (figure 2B). Certainty was very low due to bias, imprecision, and substantial inconsistency. The confidence interval includes both benefit and harm, and the absolute difference (8·95 fewer cases per 1000) was below our threshold for clinical importance, leaving the effect uncertain.

Evidence from the WHIMS RCT[4] (n=7479; mean follow-up 4·05 years) found a HR 1·76 (95% CI 1·19–2·60) for combined MHT and probable dementia in women aged 65 years or older, an absolute risk difference of 6·9 more cases per 1000 (95% CI 1·7–14·6). Certainty was moderate, downgraded for imprecision as the confidence interval includes both trivial and important harm. Given the modest absolute difference combined MHT likely results in little to no difference in dementia risk.

A meta-analysis of four observational studies[17,18,27,31] (n=693 412; follow-up 4–19 years) found a pooled RR 1·12 (95% CI 0·97 to 1·30; I^2=85·30%) for combined MHT and all-cause dementia (figure 3A), an absolute difference of 10·1 more cases per 1000 (95% CI –2·53 to 25·32). Certainty was very low due to bias, inconsistency, imprecision, and indirectness. The confidence interval spans both benefit and harm, leaving the effect uncertain.

For combined MHT versus no MHT with outcome Alzheimer's disease, a meta-analysis of five observational studies[17,18,27,29,34] (n=887 348; follow-up 6–19 years) found a pooled RR 1·11 (95% CI 1·03–1·18; I^2=39·82%) (figure 2B), an absolute difference of 23·87 more cases per 1000 (95% CI 6·51–39·06). While this exceeds the predefined threshold for an important effect, the confidence interval includes a trivial effect. Certainty was very low due to high risk of bias and imprecision, leaving the effect uncertain.

A meta-analysis of three observational studies[29,30,33] (n=209 161; follow-up 3·4–19·0 years) found a pooled RR 1·16 (95% CI 0·96–1·40; I^2=57·54%) for dementia or Alzheimer's disease with 5 years or less of oestrogen-only MHT (figure 2C). The absolute difference was 31·47 more cases per 1000 (95% CI –7·87 to 78·68). Certainty was very low due to high risk of bias and serious imprecision, leaving the effect uncertain.

A meta-analysis of three observational studies[17,29,33] (n=824 654; follow-up 6–19 years) found a pooled RR 1·16 (95% CI 0·92–1·46; I^2=96·88%) for dementia or Alzheimer's disease with 5–10 years of oestrogen-only MHT (figure 2D). The absolute difference was 31·44 more cases per 1000 (95% CI –15·72 to 90·39). Certainty was very low due to high risk of bias, inconsistency, and imprecision, leaving the effect uncertain.

A meta-analysis of four observational studies[17,29–31] (n=825 350; follow-up 3·4–16·0 years) found a pooled HR

	Country	Population of interest for GRADE	Study design	Sample size	Intervention	Comparator	Outcome	Duration of use	Age at MHT initiation	Age, mean (SD)	Follow-up period	Risk of bias
Armstrong et al (2020)[35]	USA	Post-menopausal women	Secondary analysis of two RCTs	Intervention (n=3610), treatment as usual (n=3610), total (n=7220)	Oestrogen-only MHT (hysterectomised), combined MHT (intact uterus)	Matching placebo tablet	Incident dementia or mild cognitive impairment	Not provided	65–80 years	Range 70·5–71·9 years	7·3–7·8 years	Some concerns
Espeland et al (2015)[36]	USA	Post-menopausal women	RCT	Intervention (n=3556), treatment as usual (n=3677), total (n=7233)	Oestrogen-only MHT (hysterectomised), combined MHT (intact uterus)	Matching placebo tablet	Probable dementia, probable dementia or mild cognitive impairment	4·8 (SD 1·0) to 5·9 (SD 1·5) years	≥65 years	Diabetes MHT: 71·1 years (3·7); placebo: 70·7 (3·8) years; no diabetes MHT: 71·0 years (3·8); placebo: 71·0 years (3·9)	18 years (maximum); mean=9·9 years	Low
Han et al (2021)[27]*	South Korea	Post-menopausal women	Prospective cohort study	Intervention (n=821), treatment as usual (n=12 289), total (n=13 110)	Cumulative use of tibolone, defined daily dose	Never tibolone user in lifetime	Total dementia, Alzheimer's disease, vascular dementia	4 years	From <65 years to ≥65 years	Only age at baseline is provided: 61·8 years for tibolone users, 58·2 years for non-tibolone users	9 years	High
Imtiaz et al (2017)[28]*	Finland	Post-menopausal women	Observational prospective cohort study	Cases (n=46 117), control (n=184 463), total (n=230 580)	Any MHT use (oestrogen-only MHT and combined MHT)	Non-users	Alzheimer's disease	Ranging from 11·5 months to 150 months	No information	Alzheimer's disease cases mean 54·1 years; control cases 52·0 years	20 years	Some concerns
Imtiaz et al (2017)[29]	Finland	Post-menopausal women	Observational: nested case–control within prospective cohort	Total (n=8195), cases of incident Alzheimer's disease (n=227)	Oestrogen-only MHT and combined MHT	Never users	Alzheimer's disease	Not provided	Oestrogen-only MHT: 63·8–64·1 years; combined MHT: 62·1–62·4 years (mean)	Alzheimer's disease cases mean (range): 81·5 years (76·8–85·4); control 81·5 years (76·8–85·4)	6 years	Some concerns
Manson et al (2013)[37]	USA	Post-menopausal women	Findings from the two Women's Health Initiative hormone therapy trials (RCT) with extended post-intervention follow-up	Intervention (n=13 816), treatment as usual (n=13 531), total (n=27 347)	Oestrogen-only MHT (hysterectomised), combined MHT (intact uterus)	Matching placebo tablet	Probable dementia	Combined MHT median: 5·6 years; oestrogen only median: 7·2 years	≥65 years	Aged 65 years or older at enrolment	13 years	Low
Paganini-Hill et al (2020)[30]*	USA	Post-menopausal women	Observational: prospective cohort study	Intervention (n=297), treatment as usual (n=127), total (n=424)	Oestrogen-only MHT	Never users of oestrogen before age 68·5 years	Incident dementia	No information	No information	No information	3·4 years	High
Petitti et al (2008)[31]*	USA	Post-menopausal women	Observational: prospective cohort study	Intervention (n=1519), treatment as usual (n=1387), total (n=2906)	Oestrogen-only MHT, combined MHT	Non-users of MHT	Dementia	Oestrogen-only MHT: 30·5 years; combined MHT: 23·2 years (self-reported)	Oestrogen-only MHT: 48·3 years; combined MHT 54·9 years	78·7 years	4 years	High

(Table 1 continues on next page)

	Country	Population of interest for GRADE	Study design	Sample size	Intervention	Comparator	Outcome	Duration of use	Age at MHT initiation	Age, mean (SD)	Follow-up period	Risk of bias
(Continued from previous page)												
Pourhadi et al (2021)[32]*	Denmark	Post-menopausal women	Observational: nested case–control within prospective cohort study	Intervention (n=11 667), treatment as usual (n=38 647), total (n=50 314)	Vaginal oestrogen	No systematic hormone use and no vaginally administered oestradiol from Jan 1, 1995	Dementia, Alzheimer's disease	The median cumulative dose of 1800 mcg for cases corresponds to 0·7–1·7 years of maintenance treatment and the median cumulative dose of 2050 mcg for controls corresponds to 0·8–2·0 years of maintenance treatment	63 years (median)	50–60 years at study initiation	19 years	High
Pourhadi et al (2023)[18]*	Denmark	Post-menopausal women	Observational: nested case–control within prospective cohort study	Intervention (n=17 936), treatment as usual (n=43 543), total (n=61 479)	Combined MHT	No use of MHT from the age of 45–55 years until 2 years before a dementia diagnosis or matching	All-cause dementia, Alzheimer's disease, late-onset dementia	Categorised from less than a year to more than 12 years	45 to ≥60 years (range)	Median 70 years	19 years	Low
Pourhadi et al (2024)[33]*	Denmark	Post-menopausal women	Observational: nested -case–control within prospective cohort study	Intervention (n=1505), treatment as usual (n=1129), total (n=2634)	Oestrogen-only MHT	Never users of any MHT from age 45–55 years until index date	All-cause dementia	Case: median 5·4 years; control: median 5·1 years	51–54 years (IQR)	Median 70 years	19 years	High
Shao et al (2012)[34]*	USA	Post-menopausal women	Observational: prospective cohort study	Intervention (n=1105), treatment as usual (n=663), total (n=1768)	Oestrogen-only MHT, combined MHT	Never use of any agent in lifetime	Alzheimer's disease	No information	<5 years or >5 years of menopause	MHT users: 73·4 years (5·6); non-MHT users: 76·7 (6·9)	7 years	High
Shumaker et al (2003)[5]	USA	Post-menopausal women	RCT	Intervention (n=2229), treatment as usual (n=2303), total (n=4532)	Oestrogen-only MHT (hysterectomised), combined MHT (intact uterus)	Matching placebo tablet	Probable dementia, mild cognitive impairment, Alzheimer's disease, probable dementia or mild cognitive impairment	4·7–5·9 years	≥65 years	≥65 years	4·05 years	Low
Shumaker et al (2004)[4]*	USA	Post-menopausal women	RCT	Intervention (n=5157), treatment as usual (n=5269), total (n=10 426)	Oestrogen-only MHT (hysterectomised), combined MHT (intact uterus)	Matching placebo tablet	Probable dementia, probable dementia or mild cognitive impairment	No information	≥65 years	≥65 years	8 years maximum	Low
Vinogradova et al (2021)[17]*	UK	Post-menopausal women	Observational: two nested case–control studies within a prospective cohort	Intervention (n=85 017), treatment as usual (n=530 900), total (n=615 917)	Oestrogen-only MHT, combined MHT and tibolone	No exposure more than 3 years before the index date	Dementia, Alzheimer's disease	Categorised into 1–4 years, 5–9 years, and 10 years or more	≥55 years	84 years	16 years	Some concerns

RCT=randomised controlled trial. MHT=menopause hormone therapy. *Indicates studies included in the GRADE assessment and meta-analysis.

Table 1: **Characteristics of included studies**

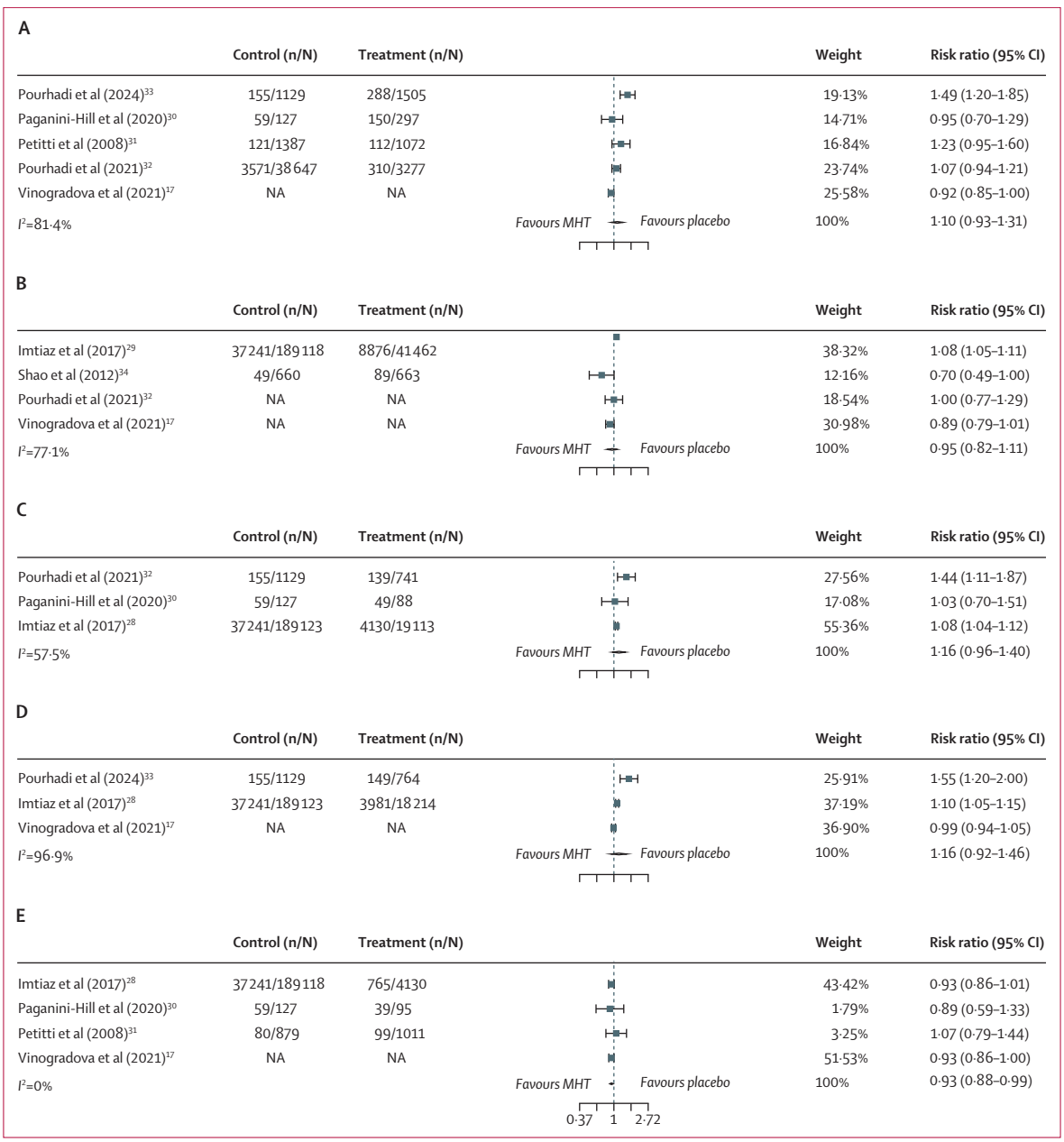
	Outcome	Number of participants and studies	Effect size (HR or RR)	Absolute effect difference	Certainty of the evidence	Summary
Oestrogen-only MHT	Probable dementia	Intervention: 1464, control: 1483 (1 RCT)	HR 1·49 (95% CI 0·83–2·66)	Difference: 6·27 more per 1000 (95% CI 2·12 fewer to 21·2 more)	Low; downgraded twice due to serious imprecision	Oestrogen-only MHT might result in little to no difference in the risk of dementia (in women receiving the treatment at age 65 years or older)
Oestrogen-only MHT	All-cause dementia or incident dementia	Intervention: 100 005, control: 572 190 (5 observational studies)	RR 1·10 (95% CI 0·93–1·31)	Difference: 9·46 more per 1000 (95% CI 6·62 fewer to 29·33 more)	Very low; downgraded due to imprecision, high risk of bias in majority of included studies, which contributed to 50·68% of the pooled effect, high inconsistency, and serious indirectness	We are uncertain about the effects of oestrogen-only MHT on dementia risk
Oestrogen-only MHT	Alzheimer's disease	Intervention: 116 390, control: 757 712 (4 observational studies)	RR 0·95 (95% CI 0·82–1·11)	Difference: 8·95 fewer per 1000 (95% CI 32·2 fewer to 19·68 more)	Very low; downgraded due to high risk of bias in some of the included studies, imprecision and high inconsistency	We are uncertain about the effects of oestrogen-only MHT on the risk of Alzheimer's disease
Combined MHT	Probable dementia	Intervention: 3693, control: 3786 (1 RCT)	HR 1·76 (95% CI 1·19–2·60)	Difference: 6·9 more per 1000 (95% CI 1·7–14·6 more)	Moderate; downgraded once due to imprecision	Combined MHT likely results in little to no difference in risk of dementia (in women receiving treatment at age 65 years or older)
Combined MHT	Probable dementia	Intervention: 105 293, control: 588 119 (4 observational studies)	RR 1·12 (95% CI 0·97–1·30)	Difference: 10·13 more per 1000 (95% CI 2·53 fewer to 25·32 more)	Very low; downgraded due to some concerns of bias in majority of included studies, high inconsistency, serious indirectness and imprecision	We are uncertain about the effects of combined MHT on dementia risk
Combined MHT	Alzheimer's disease	Intervention: 122 451, control: 774 897 (5 observational studies)	RR 1·11 (95% CI 1·03–1·18)	Difference: 23·87 more per 1000 (95% CI 6·51 more to 39·06 more)	Very low; downgraded twice due to high risk of bias in some included studies and once due to imprecision	We are uncertain about the effects of combined MHT on the risk of Alzheimer's disease
Oestrogen-only MHT for less than 5 years	All-cause dementia or incident dementia	Intervention: 200 403, control: 188 758 (3 observational studies)	RR 1·16 (95% CI 0·96–1·40)	Difference: 31·47 more per 1000 (95% CI 7·87 fewer to 78·68 more)	Very low; downgraded due to concerns of high bias in majority of included studies, and serious imprecision	We are uncertain about the effects of taking oestrogen-only MHT for less than 5 years on dementia risk
Oestrogen-only MHT for 5–10 years	Dementia	Intervention: 105 123, control: 719 531 (3 observational studies)	RR 1·16 (95% CI 0·92–1·46)	Difference: 31·44 more per 1000 (95% CI 15·72 fewer to 90·39 more)	Very low; downgraded due to concerns of high bias in majority of included studies, high inconsistency and serious imprecision	We are uncertain about the effects of taking oestrogen-only MHT for 5–10 years on dementia risk
Oestrogen-only MHT for more than 10 years	Dementia	Intervention: 105 434, control: 719 916 (4 observational studies)	HR 0·93 (95% CI 0·88–0·99)	Difference: 13·74 fewer per 1000 (95% CI 23·56 fewer to 1·96 fewer)	Very low; downgraded due to concerns of high bias in some included studies and imprecision	We are uncertain about the effect of oestrogen-only MHT taken for more than 10 years on dementia risk
Oestrogen-only MHT initiated between the age of 45–55 years	Dementia	Intervention: 4129, control: 3197 (3 observational studies)	HR 1·12 (95% CI 0·67–1·87)	Difference: 13·91 more per 1000 (95% CI 38·25 fewer to 109·83 more)	Very low; downgraded due to concerns of high bias in all included studies, high inconsistency and serious imprecision	We are uncertain about the effect of oestrogen-only MHT initiated from the ages 45–55 years on dementia risk
Oestrogen-only MHT initiated at the age ≥60 years	Alzheimer's disease	Intervention: 30 268, control: 226 149 (2 observational studies)	RR 1·08 (95% CI 1·05–1·11)	Difference: 14·32 more per 1000 (95% CI 8·95 more to 19·69 more)	Very low; downgraded due to some concerns of risk of bias in one included study out of the two included studies and imprecision	We are uncertain about the effects of oestrogen-only MHT initiated after age ≥60 years on the risk of Alzheimer's disease
Combined MHT for less than 5 years	Alzheimer's disease	Intervention: 8393, control: 199 781 (2 observational studies)	RR 1·12 (95% CI 1·07–1·17)	Difference: 22·81 more per 1000 (95% CI 13·31 to 32·32 more)	Very low; downgraded due to some concerns of risk of bias in one highly weighted study, serious indirectness	We are uncertain about the effect of taking combined MHT for less than 5 years
Combined MHT for 5–10 years	Dementia	Intervention: 92 589, control: 718 402 (2 observational studies)	RR 1·04 (95% CI 0·96–1·13)	Difference: 7·92 more per 1000 (95% CI 7·92 fewer to 25·75 more)	Very low; downgraded due to some concerns of risk of bias in included studies, high inconsistency and imprecision	We are uncertain about the effect of taking combined MHT for 5–10 years
Combined MHT for more than 10 years	Dementia	Intervention: 112 044, control: 763 332 (4 observational studies)	RR 1·24 (95% CI 0·97–1·60)	Difference: 42·62 more per 1000 (95% CI 5·33 fewer to 106·56 more)	Very low; downgraded due to high inconsistency, serious imprecision	We are uncertain about the effect of taking combined MHT for more than 10 years
Combined MHT initiated between ages 45–55 years	Dementia	Intervention: 20 560, control: 45 593 (3 observational studies)	HR 1·13 (95% CI 0·77–1·66)	Difference: 11·66 more per 1000 (95% CI 20·63 fewer to 59·2 more)	Very low; downgraded due to concerns of high risks, serious imprecision	We are uncertain about the effect of taking combined MHT initiated between ages 45–55 years

MHT=menopause hormone therapy. HR=hazard ratio. RR=risk ratio.

Table 2: **A summary of GRADE-rated evidence on the associations between MHT type, timing, and dementia outcomes**

0·93 (95% CI 0·88–0·99; I^2=0%) for dementia or Alzheimer's disease with more than 10 years of oestrogen-only MHT (figure 2E). The absolute difference of 13·74 fewer cases per 1000 (95% CI 1·96 to –23·56). Certainty was very low due to high risk of bias and imprecision, leaving the effect uncertain.

A meta-analysis of three observational studies[31,33,34] (n=7308; follow-up 4–19 years) found a pooled HR 1·12 (95% CI



(Figure 2 continues on next page)

0·67–1·87; I^2=86·35%) for dementia or Alzheimer's disease with oestrogen-only MHT initiated between 45 years and 55 years (figure 2F). The absolute difference was 13·91 more cases per 1000 (95% CI –38·25 to 100·83). Certainty was very low due to high risk of bias, inconsistency, and serious imprecision leaving the effect uncertain.

A meta-analysis of two observational studies[29,32] (n=256 417; follow-up 6–19 years) found a pooled RR 1·08 (95% CI 1·05–1·11; I^2=0%) for dementia or Alzheimer's disease with oestrogen-only MHT initiated after age 60 years (figure 2G). The absolute difference was 14·32 more cases per 1000 (95% CI 8·95–19·69). Certainty was very low due to some risk of bias and imprecision, leaving the effect uncertain.

A meta-analysis of two observational studies[27,29] (n=208 184; follow-up 6–9 years) yielded a pooled RR 1·12 (95% CI 1·07–1·17; I^2=0%) for dementia or Alzheimer's disease with combined MHT for less than 5 years (figure 3C). The absolute difference was 22·81 more cases per 1000 (95% CI 13·31 to 32·32). Certainty was very low due to some risk of bias in a highly weighted study and serious indirectness, leaving the effect uncertain.

Two observational studies[17,29] (n=810 991; follow-up 6–16 years) gave a pooled RR 1·04 (95% CI 0·96–1·13;

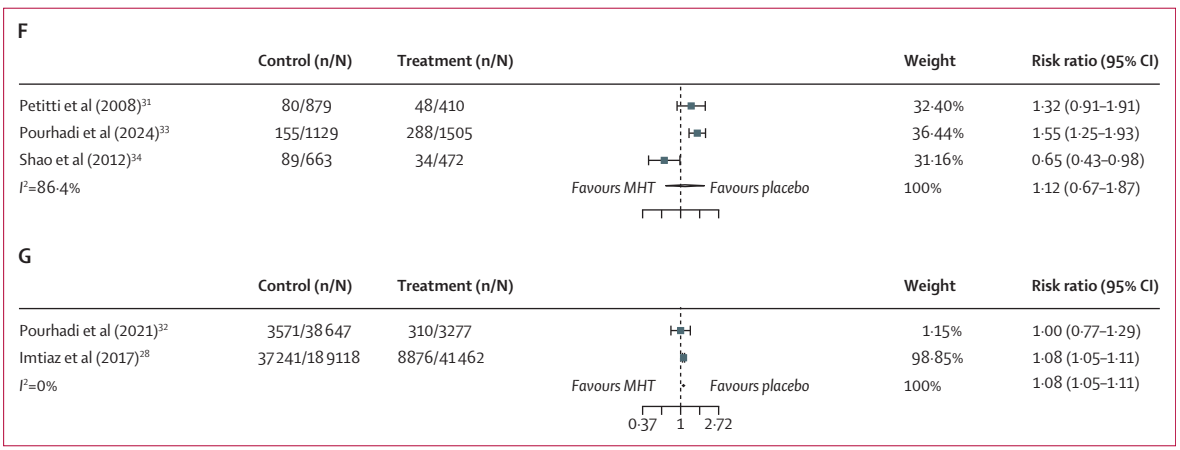


Figure 2: **Random-effects meta-analyses of oestrogen-only MHT and the risk of dementia and Alzheimer's disease, overall and by duration and timing of use**
(A) Random-effects meta-analysis of oestrogen-only MHT and the risk of all-cause dementia. (B) Random-effects meta-analysis of oestrogen-only MHT and the risk of Alzheimer's disease. (C) Random-effects meta-analysis of oestrogen-only MHT (≤5 years) and the risk of all-cause dementia or Alzheimer's disease. (D) Random-effects meta-analysis of oestrogen-only MHT (5–10 years) and the risk of all-cause dementia or Alzheimer's disease. (E) Random-effects meta-analysis of oestrogen use (>10 years) and the risk of all-cause dementia or Alzheimer's disease. (F) Random-effects meta-analysis of oestrogen only use initiated between age 45–55 years and the risk of all-cause dementia or Alzheimer's disease. (G) Random-effects meta-analysis of oestrogen only use initiated after age 60 years and the risk of all-cause dementia or Alzheimer's disease. MHT=menopause hormone therapy. NA=not available.

I^2=79·50%) for dementia or Alzheimer's disease with combined MHT for 5–10 years (figure 3D). The absolute difference was 7·92 more per 1000 (95% CI –7·92 to 25·75). Certainty was very low due to some risk of bias and high inconsistency, leaving the effect uncertain.

Four observational studies[17,18,29,31] (n=875 376; follow-up 5–19 years) produced a pooled RR 1·24 (95% CI 0·97–1·60; I^2=89·75%) for dementia or Alzheimer's disease with combined MHT for more than 10 years (figure 3E). The absolute difference was 42·62 more per 1000 (95% CI –5·33 to 106·56). Certainty was very low due to high inconsistency and serious imprecision, leaving the effect uncertain.

Three observational studies[18,31,34] (n=66 153; follow-up 5–19 years) yielded a pooled HR 1·13 (95% CI 0·77–1·66; I^2=66·84%) for dementia or Alzheimer's disease with combined MHT initiated between ages 45–55 years (figure 3F). The absolute difference was 11·66 more per 1000 (95% CI –20·63 to 59·20). Certainty was very low due to high risk of bias and serious imprecision, leaving the effect uncertain.

Discussion

The available evidence does not confirm whether MHT has a positive, negative, or null effect on the risk of dementia or mild cognitive impairment. This is consistent with previous studies[15,20] but extends this uncertainty to MHT and dementia following premature or early menopause. Additionally, this systematic review and meta-analysis confirms that there is no current evidence regarding the effect of testosterone on mild cognitive impairment or dementia. The only RCT[4] of MHT and dementia reported an increased risk with both oestrogen-only MHT (HR 1·49 [95% CI 0·83–2·66]) and combined MHT (HR 1·76 [95% CI 1·19–2·60]) in women commencing MHT aged 65 years and older, although the wide confidence intervals for oestrogen-only MHT indicate serious imprecision. Observational studies reported inconsistent associations, with very low certainty due to bias, heterogeneity, and imprecision. Timing of initiation and duration of use showed mixed and uncertain results. Overall, available evidence to date does not support MHT solely for risk reduction of dementia nor does MHT increase dementia risk. There is a need for further high-quality research to clarify the role of MHT in relation to dementia. Our findings are partly consistent with a previous systematic review and meta-analysis including six RCT reports and 45 observational studies,[39] with mixed findings: RCTs of MHT in women aged 65 years or older suggested an increased dementia risk, whereas observational data indicated a potential reduced risk, particularly for midlife oestrogen-only MHT, with an estimated 32% reduction in dementia risk. A 2025 meta-analysis by Mosconi and colleagues[40] reported an 11·3% reduced risk of Alzheimer's disease and dementia associated with MHT, especially oestrogen-only MHT initiated during midlife and sustained for longer durations, consistent with the concept of a therapeutic window for neuroprotection. We found no evidence for a therapeutic window of timing of MHT for cognitive protection. Unlike in the Mosconi study,[40] we applied risk-of-bias assessments and used stricter inclusion criteria, excluding cross-sectional studies and poorly defined case–control designs to minimise bias and overestimation of effects. We used GRADE to assess certainty and carefully reviewed overlapping cohorts. To avoid double counting, we included only one RCT from the Women's Health Initiative, whereas other reviews included six reports from four distinct trials.[39] While the reviews led by Nerattini and colleagues[39] and Mosconi and colleagues[40] suggest that MHT might be protective if initiated in midlife, we remain

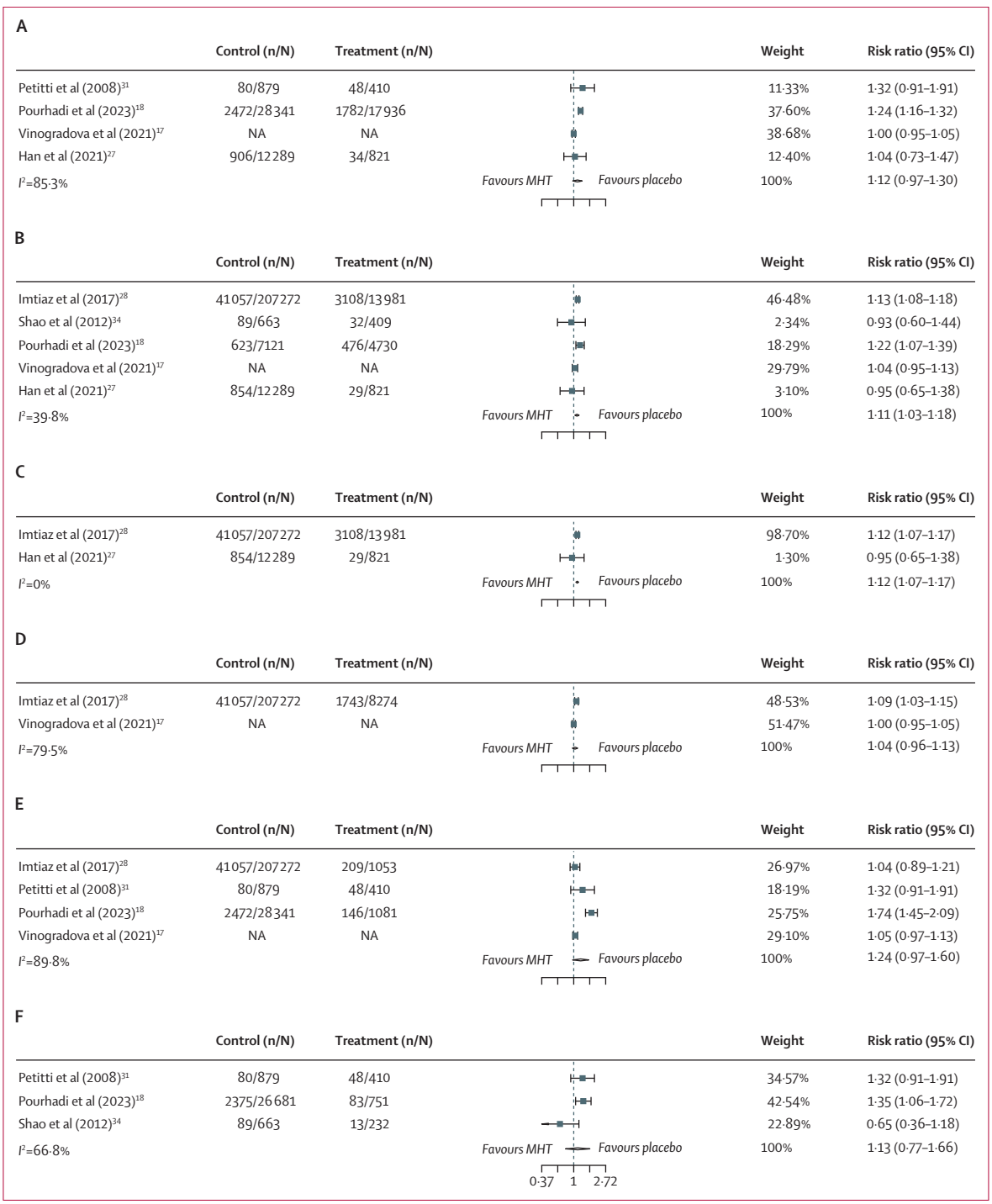


***Figure 3*: Random-effects meta-analyses of combined MHT and the risk of dementia and Alzheimer's disease, overall and by duration and timing of use**
(A) Random-effects meta-analysis of combined MHT and the risk of all-cause dementia. (B) Random-effects meta-analysis of combined MHT and the risk of Alzheimer's disease. (C) Random-effects meta-analysis of combined MHT use (≤5 years) and the risk of all-cause dementia or Alzheimer's disease. (D) Random-effects meta-analysis of combined MHT (5–10 years) and the risk of all-cause dementia or Alzheimer's disease. (E) Random-effects meta-analysis of combined MHT use (more than 10 years) and the risk of all-cause dementia or Alzheimer's disease. (F) Random-effects meta-analysis of combined MHT (initiated between age 45 and 55 years) and the risk of all-cause dementia or Alzheimer's disease. MHT=menopause hormone therapy. NA=not available.

cautious, highlighting evidence gaps and the need for further well-designed studies to clarify timing, formulation, and duration effects.

Although the European Society of Human Reproduction and Embryology 2024 guidelines recommend MHT for the prevention of dementia following premature ovarian insufficiency,[41] we found no studies to support this. Consistent with 2024 updated NICE guidelines and the Lancet Commission, we found no evidence that MHT reduced the risk of dementia after early menopause.[15] Following menopause at the average age, our findings align with the evidence presented in the NICE[20] and the US Preventive Services Task Force[42] guidelines, which indicate that MHT does not reduce dementia risk, with NICE highlighting evidence suggesting potential age-related risks.

It is important to note the limitations in this review. Only one RCT was identified that included women aged 65 years or older at MHT initiation, not reflecting common clinical practice. This trial was terminated early (after approximately 6 years) due to increased risks of non-cognitive adverse events, and high dropout rates (38–54%) that exceeded projections. Quality of life and functional outcomes were inconsistently reported across included studies.

Most evidence came from observational studies, susceptible to residual confounding, survival bias, and exposure or outcome misclassification. MHT use was often defined through prescription or self-reported data without confirmation of adherence, and dementia diagnoses were frequently based on administrative coding without specialist verification. Considerable heterogeneity existed in study design, exposure definitions, outcomes, and outcome ascertainment, limiting comparability and synthesis.

Trials including ELITE[43] and KEEPS[44,45] have assessed cognitive decline and Alzheimer's disease biomarkers as secondary outcomes in younger post-menopausal women finding neutral results. Evaluating these outcomes at earlier ages, guided by existing frameworks[46] and using complementary methods such as drug-targeted Mendelian randomisation studies,[47] might offer practical strategies for studying dementia risk when long-term RCTs are not feasible. Network meta-analyses could in principle compare MHT formulations, doses, and timing.

Despite the breadth of literature reviewed, several important gaps remain, consistent with those highlighted by NICE.[20] There were insufficient data to evaluate whether delivery method (eg, oral, transdermal, or intrauterine), type of oestrogen, progestogen or progesterone, or dose modifies the risk of mild cognitive impairment or dementia. There is an evidence gap for women from ethnic minority backgrounds, and those with pre-existing mild cognitive impairment. Potential modifying effects of genetic factors such as APOE ε4 status were not examined in this review. No data were provided for a subgroup analysis by conditions of hysterectomy or oophorectomy. Future research should differentiate participant groups by menopausal types since the effect of hysterectomy or oophorectomy itself on cognitive impairment has been widely documented.[48,49] Adverse events were not reported in observational studies, further limiting a comprehensive risk–benefit assessment.

We used a comprehensive, language-inclusive search and applied stringent inclusion criteria, restricting observational evidence to prospective cohorts, nested case-control studies, and quasi-experimental designs with adjustment for key confounders (eg, lifestyle, BMI, socioeconomic status). Risk of bias was assessed using ROBINS-E and RoB 2, with certainty of evidence evaluated via GRADE. We ensured no cohort overlap (eg, Women's Health Initiative, WHIMS, and Women's Health Initiative Memory Study of Younger Women) and interpreted findings in the context of existing RCT evidence and current clinical guidelines. Although our search comprehensively searched for studies including premature ovarian insufficiency, early menopause, mild cognitive impairment, and testosterone, no eligible studies were identified specifically addressing these subgroups or interventions. This highlights important gaps in the current evidence base, which limit evidence-based care for women. In conclusion, we found very low-certainty evidence of either a reduced or increased risk of dementia associated with MHT, for any type, duration, or initiation period.

Contributors

All authors contributed to the design of the study. Searches were done by KUK and PC. Article screening, data extraction, and risk assessments were completed by LH and MMe. Data validation was completed by LH, MMi, and MMe. LH completed the meta-analysis with support from RD and MMe. MMe completed the GRADE analysis. The manuscript was produced by MMe. The work was supervised by RD, CF, AS, MH, and PN. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MH reports funding from the National Health and Medical Research Fund of Australia, Medical Research Future Fund of Australia, Wellcome LEAP, The National Institute for Health and Care Research and meeting support from UK NICE, membership of a WHO international advisory board, board membership of BreastScreen Victoria, and an editor role at Cochrane Collaboration. All other authors declare no competing interests.

Data sharing

All data in this systematic review and meta-analysis were obtained from publicly available primary studies. Effect sizes synthesised in the meta-analysis are presented in the tables and figures. For further details regarding the data used in the analysis, please contact the corresponding author.

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References

1 Rahman A, Jackson H, Hristov H, et al. Sex and gender driven modifiers of Alzheimer's: the role for estrogenic control across age, race, medical, and lifestyle risks. *Front Aging Neurosci* 2019; **11:** 315.

2 Hogervorst E, Yaffe K, Richards M, Huppert F. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev* 2022; **3:** CD003799.

3 Zhou HH, Yu Z, Luo L, Xie F, Wang Y, Wan Z. The effect of hormone replacement therapy on cognitive function in healthy postmenopausal women: a meta-analysis of 23 randomized controlled trials. *Psychogeriatrics* 2021; **21:** 926–38.

4 Shumaker SA, Legault C, Kuller L, et al, and the Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291:** 2947–58.

5 Shumaker SA, Legault C, Rapp SR, et al, and the WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289:** 2651–62.

6 Henderson VW, Paganini-Hill A, Emanuel CK, Dunn ME, Buckwalter JG. Estrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. *Arch Neurol* 1994; **51:** 896–900.

7 Henderson VW, Espeland MA, Hogan PE. Prior use of hormone therapy and incident Alzheimer's disease in the Women's Health Initiative Memory Study. *Neurology* 2007; **68:** 205.

8 Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA, and the MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005; **76:** 103–05.

9 Kim YJ, Soto M, Branigan GL, Rodgers K, Brinton RD. Association between menopausal hormone therapy and risk of neurodegenerative diseases: implications for precision hormone therapy. *Alzheimers Dement (NY)* 2021; **7:** e12174.

10 Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol* 2011; **69:** 163–69.

11 Zandi PP, Carlson MC, Plassman BL, et al, and the Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA* 2002; **288:** 2123–29.

12 Weiderpass E, Baron JA, Adami HO, et al. Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 1999; **353:** 1824–28.

13 Akter N, Kulinskaya E, Steel N, Bakbergenuly I. The effect of hormone replacement therapy on the survival of UK women: a retrospective cohort study 1984–2017. *BJOG* 2022; **129:** 994–1003.

14 Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med* 2011; **26:** 546–50.

15 Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet* 2024; **404:** 572–628.

16 Sung YF, Tsai CT, Kuo CY, et al. Use of hormone replacement therapy and risk of dementia: a nationwide cohort study. *Neurology* 2022; **99:** e1835–42.

17 Vinogradova Y, Dening T, Hippisley-Cox J, Taylor L, Moore M, Coupland C. Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases. *BMJ* 2021; **374:** n2182.

18 Pourhadi N, Mørch LS, Holm EA, Torp-Pedersen C, Meaidi A. Menopausal hormone therapy and dementia: nationwide, nested case-control study. *BMJ* 2023; **381:** e072770.

19 Song YJ, Li S-R, Li X-W, et al. The effect of estrogen replacement therapy on Alzheimer's disease and Parkinson's disease in postmenopausal women: a meta-analysis. *Front Neurosci* 2020; **14:** 157.

20 UK National Institute for Health and Care Excellence. Menopause: identification and management. November 07 2024. https://www.nice.org.uk/guidance/ng23 (accessed Nov 27, 2025).

21 WHO. WHO handbook for guideline development, 2nd edn. World Health Organization, 2014.

22 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372:** n71.

23 Harlow SD, Gass M, Hall JE, et al, and the STRAW+10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop+10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012; **97:** 1159–68.

24 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Soft* 2010; **36:** 1–48. https://www.jstatsoft.org/index.php/jss/article/view/v036i03.

25 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998; **280:** 1690–91.

26 VanderWeele TJ. Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics* 2020; **76:** 746–52.

27 Han M, Chang J, Choi S, Cho Y, Lee G, Park SM. Association of tibolone and dementia risk: a cohort study using Korean claims data. *Gynecol Endocrinol* 2021; **37:** 567–71.

28 Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. *Neurology* 2017; **88:** 1062–68.

29 Imtiaz B, Taipale H, Tanskanen A, et al. Risk of Alzheimer's disease among users of postmenopausal hormone therapy: a nationwide case-control study. *Maturitas* 2017; **98:** 7–13.

30 Paganini-Hill A, Corrada MM, Kawas CH. Prior endogenous and exogenous estrogen and incident dementia in the 10th decade of life: the 90+ study. *Climacteric* 2020; **23:** 311–15.

31 Petitti DB, Crooks VC, Chiu V, Buckwalter JG, Chui HC. Incidence of dementia in long-term hormone users. *Am J Epidemiol* 2008; **167:** 692–700.

32 Pourhadi N, Mørch LS, Holm EA, Torp-Pedersen CT, Meaidi A. Vaginal estrogen and association with dementia: a nationwide population-based study. *Alzheimers Dement* 2022; **18:** 625–34.

33 Pourhadi N, Mørch LS, Holm EA, Torp-Pedersen C, Meaidi A. Dementia in women using estrogen-only therapy. *JAMA* 2024; **331:** 160–62.

34 Shao H, Breitner JCS, Whitmer RA, et al, and the Cache County Investigators. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology* 2012; **79:** 1846–52.

35 Armstrong NM, Espeland MA, Chen JC, et al. Associations of hearing loss and menopausal hormone therapy with change in global cognition and incident cognitive impairment among postmenopausal women. *J Gerontol A Biol Sci Med Sci* 2020; **75:** 537–44.

36 Espeland MA, Brinton RD, Hugenschmidt C, et al, and the WHIMS Study Group. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. *Diabetes Care* 2015; **38:** 2316–24.

37 Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013; **310:** 1353–68.

38 Negrini S, Arienti C, Cordani C, Kiekens C. The overview reporting map: a visual tool for overviews of systematic reviews. *J Clin Epidemiol* 2025; **185:** 111871.

39 Nerattini M, Jett S, Andy C, et al. Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. *Front Aging Neurosci* 2023; **15:** 1260427.

40 Mosconi L, Andy C, Nerattini M, et al. Systematic review and meta-analysis of menopause hormone therapy (MHT) and the risk of Alzheimer's disease and all-cause dementia: effects of MHT characteristics, location, and APOE-4 status. *Curr Obstet Gynecol Rep* 2025; **14:** 6.

41 Panay N, Anderson RA, Bennie A, et al, and the ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI. Evidence-based guideline: premature ovarian insufficiency. *Climacteric* 2024; **27:** 510–20.

42 Mangione CM, Barry MJ, Nicholson WK, et al, and the US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: US Preventive Services Task Force recommendation statement. *JAMA* 2022; **328:** 1740–46.

43 Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. *Neurology* 2016; **87:** 699–708.

44 Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. *PLoS Med* 2015; **12:** e1001833.

45 Gleason CE, Dowling NM, Kara F, et al. Long-term cognitive effects of menopausal hormone therapy: findings from the KEEPS continuation study. *PLoS Med* 2024; **21:** e1004435.

46 Bae J, Logan PE, Acri DJ, et al, and the Alzheimer's Disease Neuroimaging Initiative. A simulative deep learning model of SNP interactions on chromosome 19 for predicting Alzheimer's disease risk and rates of disease progression. *Alzheimers Dement* 2023; **19:** 5690–99.

47 Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. *J Am Soc Nephrol* 2016; **27:** 3253–65.

48 Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. *Neurodegener Dis* 2012; **10:** 175–78.

49 Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2019; **106:** 9–19.