National Institute for Health and Care Excellence

Draft for consultation

Menopause (update)

[G] Dementia

NICE guideline number tbc

Evidence review underpinning 1.6.1 (except the first two bullet points), 1.6.3 and the statements related to dementia in tables 1 and 2 as well as a research recommendation from 2015 which was retained and amended in the NICE guideline (recommendation 1.4.5 as well as research recommendations 6 and 7 are also relevant to this review but details related to these are in evidence review C)

November 2023

Draft for consultation

These evidence reviews were developed by NICE

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Review question

What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Introduction

Dementia describes a set of symptoms that occur when the brain is affected by certain diseases or conditions. These symptoms, such as memory loss and aggression, can cause distress to patients and their families, and can lead to long-term social care needs. Previous NICE guidelines (NG23, 2015) concluded that the likelihood of HRT in menopausal women affecting the risk of dementia was unknown. Recent media focus on this area has highlighted the need to clarify this. The current updated evidence review examined this question.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women, non-binary and trans people with menopause (including perimenopause and postmenopause)

Intervention	HRT*
	• Oestrogen-only
	• Combined oestrogen and progestogen
	  ○ Sequential combined
	  ○ Continuous combined
	  ○ Any combined

Comparison	• Placebo treatment • No HRT
Outcome	**Critical** • Dementia, (including where reported vascular dementia and Alzheimer's Disease) • Death due to dementia **Important** • None

HRT: hormone replacement therapy
** Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.*

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Seven studies were included for this review, 6 observational studies (Imtiaz 2017, Paganini-Hill 1996, Paganini-Hill 2020, Pourhadi 2023, Seshadri 2001, Vinogradova 2021), and 1 randomised controlled trial (RCT) reported in 3 publications (Manson 2017, Shumaker 2003, Shumaker 2004).

The studies compared oestrogen-only HRT or oestrogen plus progestogen HRT (sequential combined, continuous combined or any combined), to either no HRT, or to placebo.

The included studies are summarised in Table 2.

See the literature search strategy in Appendix B and study selection flow chart in Appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Imtiaz 2017 Finland Prospective cohort study	Postmenopausal women N=8195 Cases: n=490 Controls: 7705 Mean age (range) at baseline, years: AD: 54.1 (51.4 to 56.0) No AD: 52 (49.6 to 57.3) Mean age (range) at diagnosis, years: AD: 72.3 (59 to 78.6) Diagnosis of probable AD: DSM-IV criteria and NINCDS-ADRDA. Main criteria were progressive	Oestrogen-only Oestrogen plus progestogen (any combined)	No HRT	• Dementia: ○ Alzheimer's disease	Confounder adjustments: Age, BMI, alcohol, smoking, physical activity, occupation status, number of births, menopause status, any cancer, surgery. No information on ApoE genotype.

Study	Population	Intervention	Comparison	Outcomes	Comments
	decline in memory and cognition. Diagnosis supported by abnormal MRI or CSF biomarker findings.				
Manson 2017 United States Randomised controlled trial; WHI	Postmenopausal women Oestrogen-only: N=10739 Intervention: 5310 Placebo: 5429 Oestrogen plus progestogen: N=16608 Intervention: n=8506 Placebo: n=8102 Overall mean age not reported but provided by study group: Mean age at trial entry (age at screening) – combined HRT, years (SD): Intervention: 63.2 (7.1) Comparison: 63.3 (7.1) Mean age at trial entry (age at screening) – oestrogen-only HRT, years (SD): Intervention: 63.6 (7.3) Comparison: 63.6 (7.3)	Oestrogen-only Oestrogen plus progestogen (continuous combined)	Placebo	• Death due to dementia Duration of HRT use during the trial • Oestrogen-only: 7.2 years (median) • Oestrogen plus progestogen: 5.6 years (median)	No information on ApoE
Paganini-Hill 1996 United States	Postmenopausal women. N=1439 Cases: n=246 Controls: n=1193	Oestrogen-only	No HRT	• Dementia: ○ Alzheimer's Disease, senile dementia, dementia or senility	Confounder adjustments: Oestrogen use, age at menarche, weight, type of menopause (natural vs

Study	Population	Intervention	Comparison	Outcomes	Comments
Prospective cohort study (nested case control)	Mean age: Age at enrolment not reported. Dementia diagnosis ascertained from death certificates.				surgical), age at last menstrual period, use of blood pressure medication. No information on ApoE
Paganini-Hill 2020 United States Prospective cohort study	Postmenopausal women N=424 Cases: n=209 Controls: n=215 Mean age, years (SD): Total participants: 93.2 (2.6). Age split by group not reported. Dementia diagnosed by neurological examination by a trained physician or nurse practitioner, and a neuropsychological test battery that included the Mini-Mental State Examination.	Oestrogen-only	No HRT	• Dementia	Confounder adjustments: Education No information on ApoE
Pourhadi 2023 Denmark Retrospective cohort study (nested case-control)	N= 61470 women Cases of dementia: n=5589 Controls: = 55890 Median age at dementia diagnosis (IQR): Cases: 70 (66 to 73) Controls: 70 (66 to 73)	Oestrogen plus progestogen (any combined, continuous combined, sequential combined)	No HRT	• Dementia: ○ All-cause dementia	Confounder adjustments: Education, income, cohabitation, hypertension, diabetes, thyroid disease No information of ApoE

Study	Population	Intervention	Comparison	Outcomes	Comments
	A woman was considered a case with all cause dementia from the date (index date) of first dementia diagnosis (the 10th revision of the International Classification of Diseases (ICD-10) or from the date of redeeming first drug specific to dementia.				
Seshadri 2001 United Kingdom Retrospective cohort study (nested case-control)	Postmenopausal women N=280 Cases: n=59 Controls: n=221 Mean age: Cases: 66.7 Controls: 65.2 SD not reported Dementia diagnosis based on NINCDS-ADRDA criteria. Impairment of memory and cognition. Diagnosis was concurred between reviewing neurologists and the consulting specialists.	Oestrogen-only Oestrogen plus progestogen (any combined)	No HRT	• Dementia: ○ Alzheimer's disease	Confounder adjustments: smoking and BMI No information on ApoE genotype
Shumaker 2003 and 2004 United States Randomised controlled trial; WHIMS (sub-trial	Postmenopausal women Oestrogen-only N=2946 Intervention, n=1464 Control, n=1483 Oestrogen plus progestogen N=4532	Oestrogen-only Oestrogen plus progestogen (progestin) (continuous combined)	Placebo	Dementia	No information on ApoE genotype

Study	Population	Intervention	Comparison	Outcomes	Comments
from WHI)	Intervention, n=2229 Control, n=2303 Mean age, SD – not reported. Age range: 65 to 79 Evaluation by a physician and diagnosis using DSM-IV criteria for probable dementia. Suspected probable dementia participants then underwent computed tomography scan and blood tests to rule out reversible causes of dementia.				
Vinogradova 2021 United Kingdom Retrospective cohort study (nested case-control)	Postmenopausal women N=615917 Cases: n= 118501 Controls: n=497416 Age, mean (SD): QResearch database: Cases: 83.8 (6.6) Control: 83.5 (6.3) CPRD database: Cases: 83.0 (7.5) Control: 82.6 (7.3) Cases were ascertained from diagnosis of dementia in general practice records. Diagnosis in	Oestrogen-only Oestrogen and progestogen (any combined)	No HRT	• Dementia	Confounder adjustments: smoking, alcohol consumption, deprivation score, BMI, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other drugs, and years of data. No information on ApoE genotype

Study	Population	Intervention	Comparison	Outcomes	Comments
	secondary care based on memory clinics staffed by specialists. Diagnosis in general practice using computed tomography and supported by specialists.				

AD: Alzheimer's Disease; ApoE: apolipoprotein E; BMI: body mass index; CPRD: Clinical Practice Research Datalink; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HRT: hormone replacement therapy IQR: interquartile range; NINCDS-ADRDA: National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related disorders Associations; QResearch: name of a large consolidated UK database derived from anonymised health records; WHI: Women's Health Initiative; WHIMS: Women's Health Initiative Memory Study

See the full evidence tables in Appendix D and the forest plots in Appendix E.

Summary of the evidence

For this review outcomes have been judged for clinical importance based on statistical significance. Please see Supplement 1 for further details.

Across the observational studies, evidence was available for hormone replacement therapy by duration of use, for an unknown recency (whether current or past user) in some studies, and past users for 1 study. There was evidence available for current users of hormone replacement therapy, however their duration of use was unknown.

Most of the studies could not be pooled due to differences in the outcomes, mainly by duration of HRT use and the recency of use.

Comparison 1: Oestrogen plus progestogen, any combined, versus no HRT

Duration of HRT use, unknown recency

Across the 2 observational studies comparing oestrogen plus progestogen HRT users to non-users, very low to low quality evidence showed no important difference in risk of dementia between groups, at different durations of use, with unknown recency, ranging from less than 1 year use to 10 or more years use. The exception was low quality evidence of important increased risk of dementia for oestrogen plus progestogen users from 1 study, for those who had used oestrogen plus progestogen for less than 1 year (the other study showed no important difference for 1 year or less with very low quality rating).

Duration of HRT use, past users

Very low quality evidence from 1 study for current users of oestrogen plus progestogen HRT with unknown duration of use showed no important difference in risk of dementia between users and non-users. Very low and low quality evidence from 1 study for past users, of more than 8 years since last use, showed an important harm (increased risk of dementia) for users if duration of use was 1 year or less and up to 12 years of use (or longer).

Progestogenic constituent, mode of administration and age at first use

The evidence was also analysed according to progestogenic constituent, mode of administration and age at first use. Very low quality evidence from 1 study indicated no

important difference in risk of dementia between oestrogen plus progestogen users and non-users in any of these subgroups.

Comparison 2: Oestrogen plus progestogen, continuous combined, versus no HRT

Very low quality evidence from 1 observational study showed that for past users of HRT, of more than 8 years since the last use, there was no important difference in risk of dementia when compared to no HRT on risk of dementia if duration of use was more than 1 to 4 years, but a harm if duration of use was 1 year or less, and over 4 years use.

Comparison 3: Oestrogen plus progestogen, sequential combined, versus no HRT

Very low quality evidence from 1 observational study showed that for past users of HRT, of more than 8 years since the last user, there was an important harm (increased risk of dementia) for users if duration of use was 1 year or less and up to 8 years, and longer.

Comparison 4: Oestrogen plus progesterone, continuous combined, versus placebo

Moderate quality evidence from a randomised trial comparing oestrogen plus progestogen and placebo showed an important harm in relation to higher dementia incidence for oestrogen plus progestogen (at 5 to 7 years follow-up), but no important difference in mortality from Alzheimer's or dementia (at 18 years follow-up).

Comparison 5: Oestrogen-only versus no HRT

Duration of HRT use

Across the 2 observational studies comparing oestrogen-only users to non-users, most of the very low to low quality evidence showed no important difference in risk of dementia between groups at different durations of use ranging from less than 1 year to 10 or more years' use.

Recency of HRT use

Very low quality evidence from 1 study for current users of oestrogen-only HRT with unknown duration of use showed no evidence of important difference in risk of dementia between users and non-users.

HRT constituent, mode of administration and age at first use

The evidence was also analysed according to constituent, mode of administration and age at first use. There was very low quality evidence of no important difference in risk of dementia between oestrogen users and non-users in all these subgroups.

Comparison 6: Oestrogen-only versus placebo

Moderate quality evidence from a randomised controlled trial showed no important difference in the incidence of dementia between oestrogen-only users and placebo groups (at 5 to 7 years follow-up), but an important benefit in lower incidence of mortality from Alzheimer's or dementia for oestrogen-only HRT (at 18 years follow-up).

See Appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose dementia and death due to dementia as the critical outcomes for this review. They agreed that there was uncertainty in current practice over whether HRT reduces or increases the risk of developing dementia, and subsequent death from dementia. The committee wanted to know whether there were any differences in risk from taking HRT depending on past and current use, type of HRT used (combined or oestrogen-only), duration of use, and age at initiating HRT. The committee were also interested in the different constituents of HRT and the mode of administration. They agreed that it was important to look at the outcomes stratified by these subgroups.

The quality of the evidence

The evidence ranged from very low to moderate quality. Some of the evidence was downgraded due to study design when the evidence was a case-control study, due to inherent bias in this study design regarding selection of cases and controls. Bias in selection could either over-estimate the risk of dementia in the case group or under-estimate the effect size depending on whether the cases and controls carried different risks of dementia (this risk is not known in the studies). Most of the evidence was also downgraded due to risk of bias in observational studies. Reasons for bias were due to not adjusting for all the appropriate confounders, and also bias when use of HRT was based on prescription data as an issued prescription does not necessarily mean the woman took the HRT. Some of the evidence was also downgraded for imprecision as event numbers were small resulting in relatively wide confidence intervals for effect estimates. There was also some heterogeneity in the evidence for some subgroups.

Benefits and harms

The committee discussed that most of the evidence was very low to low quality, with some of the evidence at moderate quality. They acknowledged that most of the evidence was from observational studies and therefore adjustments for various confounders needed to be carefully considered. The committee discussed that socioeconomic status was an important confounder to consider in the case of dementia. They noted that some of the evidence was from the US setting in a population with high socioeconomic status and it is unclear how generalisable those findings would be to other populations. The committee agreed they could not reliably use this evidence to support recommendations. The committee also discussed the differences in dementia diagnosis across the studies. They discussed that some of the

evidence came from a study where dementia diagnosis was taken from death certificates which was an unreliable way of ascertaining incidence of dementia due to variable reporting therefore introducing bias into the evidence. They agreed that this was another reason for not using some of the evidence to support recommendations. The committee discussed the 2 largest observational studies were from Denmark and the UK and they had both made appropriate adjustments for many important confounders and could be used to support recommendations, as well as the randomised controlled data from the Women's Health Initiative, in particular the sub-study of the Women's Health Initiative RCT (the Women's Health Initiative Memory Study - WHIMS). They also noted that a Finnish observational study had made appropriate adjustments for many confounders, but the sample size was considerably smaller compared to the large UK and Danish studies. They agreed to focus on the large observational studies and the RCT evidence to guide their discussions and support their recommendations.

Oestrogen plus progestogen versus no HRT or placebo

The committee discussed the evidence by comparison. They discussed the evidence for combined oestrogen and progestogens compared to no HRT or placebo and noted that 2 large, nested case control studies were part of the evidence base for this comparison. They agreed that the results of these 2 studies (for the reasons described above), as well as RCT data, would largely influence their decision-making as the sample size of the other evidence was considerably smaller. They also made adjustments for more of the important confounders.

The committee discussed that the evidence from these two observational studies was inconsistent. They noted that one study showed no difference between oestrogen plus progestogen use and no HRT on incidence of dementia with different durations of use, whereas evidence from the other study showed an increase in incidence of dementia with oestrogen plus progestogen use when compared to no HRT, and the risk increased as duration of use increased. They also discussed that a duration of use of less than a year could be too short a duration of exposure to make a difference to dementia risk. The committee discussed that although the recency of use was not presented in the evidence showing no differences between oestrogen plus progestogen and no HRT, and could include current and past users, the evidence available for past users showed a harm. However, they agreed that they did not have evidence to describe the pattern of risk in current users and were unable to make a comment as to whether the differences in risk seen in the evidence were attributable to the recency of use. The committee agreed it was important to explore why some of the evidence was pointing to an increased risk in dementia with longer durations of HRT use. Both these studies were observational studies, and confounders needed to be carefully adjusted for to remove bias (see discussion of the RCT evidence below). They discussed that there are several known factors that are related to dementia incidence, for example lifestyle factors such as smoking and alcohol use, BMI, level of education, socioeconomic status, and loneliness. They discussed that although both studies adjusted for many relevant confounders, neither adjusted for all the main confounders. They concluded that the evidence might be at risk of bias due to confounding.

The committee also discussed possible differences in the studies due to bias by 'indication for treatment' (whether HRT was given for menopause symptoms or for other reasons) about which there was no further information. The committee noted that the evidence was for all types of dementia. They discussed that the risk for some types of dementia may be different to others, and that the proportion of each type in each study population may differ and therefore explain some of the differences seen in the risk. However, since the evidence was not available for all the different types of dementia, the committee agreed they could not comment further on this. The committee discussed the different populations in the 2 studies, and that one study was from a UK cohort, and the other in a Danish cohort. Although both the UK and Denmark are high-income setting countries, lifestyle factors and healthcare systems may differ between them. However, again the committee agreed it was difficult to

identify what the relevant differences could be in relation to risk of incidence of dementia. The committee noted that both studies were large, but the larger study was from the UK setting, and that showed no difference in risk of dementia between users and non-users of HRT.

The committee discussed the evidence from the randomised controlled trial sub-study data from oestrogen plus progestogen compared to placebo and noted that there was a statistically significant increase in risk of dementia for the HRT arm. The committee discussed that this evidence was contradictory to the evidence from UK observational data, but in line with the evidence from the study from Denmark. The committee discussed that the start age of HRT was 65 or more from the WHMIS trial and agreed that it was important to highlight this.

The committee were not unanimous in their interpretation of the evidence and how to formulate a recommendation best reflecting the evidence base. It is to be noted that some of the committee had concerns about highlighting a risk in dementia when evidence from a UK setting showed no difference in risk across all the durations of use, suggesting there was no gradient by duration of use. They discussed that because this was contradictory to observational evidence from Denmark showing a gradient by duration of use, and there was no RCT evidence available to address the discordance, they could not comment on the risk related to the duration of use in the recommendations. However, the committee used the RCT evidence to address the discordance between the observational studies, to reach a majority decision that the evidence suggested an increased risk in dementia, in combined HRT users when HRT was started after the age of 65. They agreed it was important to highlight in the recommendations that the increased risk of dementia with HRT use might be related to the age at starting of 65 years or older..

They agreed that women who are considering HRT use for troublesome menopause symptoms associated with the menopause should be made aware of the potential risk and given all the relevant information necessary so that they can make an informed decision.

The committee looked at subgroup analysis for the mode of administration and type of progestogen. The evidence for oestrogen plus progestogen showed no differences between users and non-users of HRT. The committee discussed that the evidence for these subgroups came from the UK study that showed an overall no difference in dementia risk. They agreed that without subgroup evidence from the study from Denmark, they were unable to confidently make a recommendation.

The committee discussed the evidence for mortality due to Alzheimer's or dementia which showed no statistical significance between the two arms. The committee had the same concerns about the reliability of reporting deaths due to dementia, and agreed they could not confidently say that there was no increase or decrease risk in mortality due to dementia with HRT.

Oestrogen-only versus no HRT or placebo

The committee then looked at oestrogen-only versus no HRT for the observational studies. They discussed that there were no statistically significant differences in the evidence, of various durations of use, for this comparison in terms of incidence of dementia.

The committee discussed the evidence from the randomised controlled trial sub-study that also showed no statistically significant differences for incidence of dementia, between oestrogen-only users and placebo. They discussed that the randomised controlled trial data was slightly different from typical users of HRT in that the population in the study were 65 or older when they first started using HRT. The committee discussed that for this age group, indications for HRT were less likely to be for menopause symptoms, and although not an indication for its use in the UK, more likely to be for prevention of other diseases.

The committee agreed that although there was not enough information to inform recency of use, they should still recommend for women to be informed that there was no increase in risk of dementia for oestrogen-only users of HRT.

The committee also discussed the evidence on the subgroups for mode of administration and type of oestrogen. In line with the evidence on the various durations of oestrogen-only use, the subgroup evidence also showed no statistically significant differences between users and non-users of HRT on the risk of dementia. The committee agreed that it would be useful for practitioners who prescribe HRT if the recommendations highlighted that oestrogen-only HRT does not appear to increase dementia risk.

They discussed the scope of this guideline, and that the indication for HRT prescriptions in the UK were for menopausal symptoms associated with menopause. However, they discussed that there may be a misconception that HRT provided protective effects against the risk of dementia and agreed it was important to highlight that the evidence did not support this statement and made a recommendation to not offer HRT for prevention of dementia.

The committee discussed the evidence for mortality due to Alzheimer's or dementia. The evidence showed a statistically significant benefit in terms of Alzheimer's or dementia related mortality for oestrogen-only users when compared to placebo. The committee discussed that this reduction in deaths for the oestrogen-only group was not easily explained since the evidence does not show a reduction in incidence of dementia. They discussed underreporting of deaths due to dementia in practice, as well as the difficulties of attributing deaths specifically to dementia when there may be other causes to consider. They were not confident that the evidence supported a recommendation for advice regarding the risk of mortality due to dementia.

Research recommendations

The committee noted that there are still uncertainties and further research is needed to add to the current evidence base. The research recommendation from the 2015 guideline for this topic was retained but reworded from 'What are the effects of early HRT use on the risk of dementia?' to 'What are the effects of HRT use on the risk of dementia?' The committee decided to remove 'early' because it is difficult to define what 'early' means in the context of taking HRT for menopause symptoms and also because there is still relatively little research addressing this topic so keeping the question broad would encourage more research than restricting it to 'early HRT' only.

Despite a lack of evidence relating to transgender men and non-binary people the committee agreed that the evidence was generalisable to those who have never taken gender affirming hormone therapy but were uncertain about transgender people who have taken gender affirming hormone therapy in the past and no evidence was identified for this group. They also noted that there was no evidence for people from minority ethnic family backgrounds. They agreed to make research recommendations for these groups to fill this evidence gap. The descriptions of the research recommendations can be found in appendix K of evidence report C.

Cost effectiveness and resource use

No previous economic evidence was identified for this topic.

The recommendations made for this review topic centre around the impact of HRT on the risk of developing dementia. Whilst recommendations in this area will lead to people being better informed about treatment decisions around HRT it is unclear how such information will change treatment decisions in current practice and how these will impact upon overall resource use. The committee agreed that those considering HRT and those taking HRT

should be fully aware of the risks and benefits, even if this led to an increase in resource use through changes in treatment decisions.

Other factors the committee took into account

Whilst it is unclear how HRT might affect long term health outcomes (such as breast and endometrial cancer, CVD, and stroke) in trans men and non-binary people who have previously taken as gender affirming hormone therapy because evidence is lacking, the committee agreed that it is important to improve access to services for them. They therefore recommended that it should be ensured that they can discuss their menopause symptoms with a healthcare professional with expertise in menopause. The discussion of this is described in further detail in 'the committee's discussion and interpretation of the evidence' section of evidence review C.

The committee noted that there are recommendations related to the prevention of dementia in the NICE guideline on dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset and cross referred to it, so that readers are aware of this.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 (except the first two bullet points), 1.6.3 and the statements related to dementia in tables 1 and 2 in the NICE guideline. It also supports an overarching recommendation related to trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past (recommendation 1.4.8 – see evidence review C).

The research recommendation from the 2015 guideline for this topic was retained but reworded from 'What are the effects of early HRT use on the risk of dementia?' to 'What are the effects of HRT use on the risk of dementia?'

Additionally, there are overarching research recommendations related to all health outcomes addressed in this guideline update (including dementia), for:

- trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

References – included studies

Effectiveness

Imtiaz 2017

Imtiaz, Bushra, Tuppurainen, Marjo, Rikkonen, Toni et al. (2017) Postmenopausal hormone therapy and Alzheimer disease: A prospective cohort study. Neurology 88(11): 1062-1068

Women's Health Initiative – (WHI)
Manson 2017

Manson, JoAnn E, Aragaki, Aaron K, Rossouw, Jacques E et al. (2017) Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA 318(10): 927-938

Paganini-Hill 1996

Paganini-Hill, A and Henderson, V W (1996) Estrogen replacement therapy and risk of Alzheimer disease. Archives of internal medicine 156(19): 2213-7

Paganini-Hill 2020

Paganini-Hill, A; Corrada, M M; Kawas, C H (2020) Prior endogenous and exogenous estrogen and incident dementia in the 10th decade of life: The 90+ Study. Climacteric : the journal of the International Menopause Society 23(3): 311-315

Seshadri 2001

Seshadri, S, Zornberg, G L, Derby, L E et al. (2001) Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Archives of neurology 58(3): 435-40

Vinogradova 2021

Vinogradova, Yana, Dening, Tom, Hippisley-Cox, Julia et al. (2021) Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases. BMJ (Clinical research ed.) 374: n2182

Women's Health Initiative Memory Study (WHIMS)

Shumaker 2003

Shumaker, Sally A, Legault, Claudine, Kuller, Lewis et al. (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291(24): 2947-58

Shumaker 2004

Shumaker, Sally A, Legault, Claudine, Rapp, Stephen R et al. (2003) 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 289(20): 2651-62

Appendices

Appendix A Review protocols

Review protocol for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362348
1.	Review title	Effects of hormone replacement therapy for menopausal symptoms on developing Dementia
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?
3.	Objective	To update the recommendations in NG23
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • INAHTA • HTA via CRD • PsycInfo Searches will be restricted by:

ID	Field	Content
		• Date (2015 to date) • English language only • Human studies only • RCTs, Systematic Reviews and Cohort Studies The full search will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	Menopause
6.	Population	Women, non-binary and trans people with menopause (including perimenopause and postmenopause)

7.	Intervention	HRT*
		• Oestrogen only
		• Combined oestrogen and progestogen
		  ○ Sequential combined
		  ○ Continuous combined
		• Any combined
		* Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.

8.	Comparator	• Placebo treatment • No HRT
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs • Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies.

ID	Field	Content
		Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
10.	Other exclusion criteria	• People with premature ovarian insufficiency • People with early menopause (aged 40 to 44) If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness. Observational studies will need to control for confounders Relevant confounders may include: BMI, family history, ApoE-4 genotype, lifestyle factors (smoking or alcohol intake), diabetes, hypertension, cholesterol levels, education, socioeconomic status)
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• Dementia, (including where reported vascular dementia and Alzheimer's Disease) • Death due to dementia
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the

ID	Field	Content
		full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials • ROBINS-I for non-randomised, controlled/cohort studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios or hazard ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: Mortality: statistical significance Serious intervention-related adverse effects: statistical significance

ID	Field	Content
		Validated scales/continuous outcomes: published MIDs where available All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.

17.	Analysis of sub-groups	Evidence will be stratified (in 2 layers) by:
		• Recency of HRT use (current users, < 5 years, 5-9 years, ≥ 10 years since last use)
		• by duration of HRT use (<1 year, 1-4 years, 5-9 years, 10-14 years, ≥ 15 years)
		
		Additional stratification will be done only for a single specified duration and recency of HRT use (for example: only current HRT users with 5 to 14 years of use) and will only be possible if evidence is reported in this way. Evidence will be stratified by:
		• Age at first use (45-50 years, 50-59 years, 60-69 years, >69 years)
		• Time since menopause at first use (<1 year, 1-4 years, 5-9 years, >10 years)
		• Constituent (equine oestrogen, oestradiol)
		• Mode of administration (oral, transdermal)
		• Progestogenic constituent (for combined HRT only: (Levo)norgestrel, Norethisterone acetate, Medroxyprogesterone acetate, Micronised progesterone, any synthetic progestin)
		• Length of cycle (for sequential combined HRT only: Sequential long cycle [3 monthly], Sequential 30 day cycle)
		• By surgical menopause (surgical menopause, no surgical menopause)
		• BMI (<18.5, 18.5 to 24.9, ≥25)
		• By factors identified in the equalities section of the scope:
		  ○ Ethnicity (White British, Asian/Asian British, Black/African/Caribbean/Black British, Mixed/Multiple ethnic groups)
		  ○ Disability (disability, no disability)
		  ○ Socioeconomic group (deprived, non deprived)

ID	Field	Content			
		○ Non-binary and trans people Where evidence is stratified or subgrouped, the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	27th September 2022			
22.	Anticipated completion date	23rd August 2023			
23.	Stage of review at time of this submission	Review stage	Started	Completed	
		Preliminary searches	☑	☑	
		Piloting of the study selection process	☑	☑	
		Formal screening of search results against eligibility criteria	☑	☑	
		Data extraction	☑	☑	

ID	Field	Content		
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact Guideline development team NGA 5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	Senior Systematic Reviewer Systematic Reviewer		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].		
29.	Other registration details	None		

ID	Field	Content	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=362348	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Menopause	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review questions: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing dementia?

A combined literature search was conducted for the following review questions:

C What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

D What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

E What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing endometrial cancer?

F What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?

G What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing dementia?

H What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

I What are the effects of hormone replacement therapy taken by women, non-binary and trans people with early menopause (aged 40 to 44) on all-cause mortality and developing:

- **venous thromboembolism**
- **cardiovascular disease**
- **type 2 diabetes**
- **breast cancer**
- **endometrial cancer**
- **ovarian cancer**
- **osteoporosis**
- **dementia**
- **loss of muscle mass and strength?**

Clinical searches

Database: Ovid MEDLINE(R) ALL <1946 to September 30, 2022>

Date of last search: 03/10/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	56226
3	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
4	("change of life" or life change?).ti,ab.	3175
5	or/1-4	117224
6	exp Hormone Replacement Therapy/	26181
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129

#	Searches	
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Estrogens/	97369
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	8328
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
14	or/6-13	300800
15	5 and 14	38439
16	exp Breast Neoplasms/	331829
17	exp "Neoplasms, Ductal, Lobular, and Medullary"/	45099
18	exp breast/ and exp neoplasms/	31705
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	412638
20	exp uterine neoplasms/	143954
21	Endometrial Hyperplasia/	3751
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	71639
23	exp Ovarian Neoplasms/	92941
24	Fallopian Tube Neoplasms/	3090
25	Peritoneal Neoplasms/	16848
26	Pelvic Neoplasms/	7356
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	134115
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	18696
29	exp Dementia/	195885
30	(amentia* or dementia* or lewy body).ti,ab.	131539
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	172723
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	212540
33	Death/ or exp Mortality/	438343
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	2676396
35	exp Cardiovascular Diseases/	2652417
36	exp Stroke/	164004
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	265024
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	391497
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	237740
40	(stroke or strokes).ti,ab.	293720
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	177232
42	TIA.ti,ab.	9584
43	(myocardial adj2 infarct*).ti,ab.	215115
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	85723
45	atrial flutter*.ti,ab.	6330
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	150990
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	23385
48	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/	98814
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	110885

#	Searches	
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201
52	exp Bone Remodeling/ or Bone Density/	118506
53	exp radius fractures/ or spinal fractures/ or hip fractures/	45889
54	(osteoporo* or osteop?en*).ti,ab.	91147
55	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	136427
56	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	76474
57	exp Muscle Strength/ or Muscle Contraction/ or Muscle, Skeletal/ or Muscle weakness/	275399
58	exp Muscular Atrophy/	20100
59	(sarcop?en* or dynap?eni*).ti,ab.	12753
60	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	89183
61	exp Diabetes Mellitus, Type 2/	162254
62	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	178683
63	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	3367
64	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1079
65	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	11970
66	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	52630
67	or/16-66	7071734
68	15 and 67	24780
69	animals/ not humans/	5018518
70	exp Animals, Laboratory/	944064
71	exp Animal Experimentation/	10221
72	exp Models, Animal/	633340
73	exp Rodentia/	3486788
74	(rat or rats or mouse or mice).ti.	1413148
75	or/69-74	6058843
76	68 not 75	22173
77	limit 76 to english language	19974
78	Climacteric/	4935
79	Menopause/ or Perimenopause/ or Postmenopause/	56226
80	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
81	("change of life" or life change?).ti,ab.	3175
82	or/78-81	117224
83	exp Hormone Replacement Therapy/	26181
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
86	exp *Estrogens/	97369
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
89	((combin* or sequen* or continu*) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	6337
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
91	or/83-90	300359
92	82 and 91	38419
93	animals/ not humans/	5018518
94	exp Animals, Laboratory/	944064
95	exp Animal Experimentation/	10221
96	exp Models, Animal/	633340
97	exp Rodentia/	3486788
98	(rat or rats or mouse or mice).ti.	1413148

#	Searches	
99	or/93-98	6058843
100	92 not 99	34708
101	limit 100 to english language	30818
102	randomized controlled trial.pt.	578276
103	controlled clinical trial.pt.	95066
104	pragmatic clinical trial.pt.	2153
105	randomi#ed.ab.	690521
106	placebo.ab.	232230
107	randomly.ab.	392671
108	Clinical Trials as topic.sh.	200427
109	trial.ti.	271569
110	or/102-109	1520899
111	COMPARATIVE STUDIES/	1911627
112	FOLLOW-UP STUDIES/	687669
113	TIME FACTORS/	1228326
114	reviewed.tw.	604810
115	prospective$.tw.	826138
116	retrospective$.tw.	951729
117	baseline.tw.	681295
118	cohort.tw.	716940
119	case series.tw.	96297
120	or/111-119	5840666
121	COHORT STUDIES/	319704
122	FOLLOW-UP STUDIES/	687669
123	LONGITUDINAL STUDIES/	160686
124	PROSPECTIVE STUDIES/	640096
125	RETROSPECTIVE STUDIES/	1062925
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	990520
127	(incidence? adj (stud* or research or analys*)).tw.	2167
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	8189
129	(prospective* adj method*).tw.	492
130	(retrospective* adj design*).tw.	2556
131	Case-Control Studies/	323880
132	"nested case control".ti,ab.	10276
133	or/121-132	2937576
134	110 or 120 or 133	7274173
135	101 and 134	16133
136	77 or 135	25292

1

2 Database: Embase <1974 to 2022 September 30>

3 Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537

#	Searches	
9	exp *estrogen/	126164
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
14	or/6-13	401114
15	5 and 14	58995
16	exp breast tumor/	610160
17	exp medullary carcinoma/	11738
18	exp breast/ and exp neoplasm/	81181
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	580028
20	exp uterus cancer/	178703
21	endometrium hyperplasia/	8475
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	94083
23	exp ovary tumor/	165879
24	uterine tube tumor/	1128
25	exp peritoneum tumor/	32297
26	exp pelvis tumor/	8687
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	189064
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	26375
29	exp dementia/	414481
30	(amentia* or dementia* or lewy body).ti,ab.	188972
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	233156
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	296024
33	death/ or fatality/ or exp mortality/	1565750
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	3638723
35	exp cardiovascular disease/	4653676
36	exp cerebrovascular accident/	278318
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	395575
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	582395
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	388936
40	(stroke or strokes).ti,ab.	467280
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	248980
42	TIA.ti,ab.	21167
43	(myocardial adj2 infarct*).ti,ab.	308381
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	151993
45	atrial flutter*.ti,ab.	10322
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	225615
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	38407
48	pulmonary embolism/ or lung embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or vein thrombosis/ or upper extremity deep vein thrombosis/	238572
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	173070

#	Searches	
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963
53	(osteoporo* or osteop?en*).ti,ab.	139235
54	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	184524
55	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	105447
56	muscle strength/ or muscle contraction/ or skeletal muscle/ or muscle weakness/	298183
57	exp muscle atrophy/	53010
58	(sarcop?en* or dynap?eni*).ti,ab.	19831
59	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	123477
60	diabetes mellitus/ or non insulin dependent diabetes mellitus/	903538
61	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	274466
62	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	4587
63	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1729
64	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	13941
65	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	87957
66	or/16-65	10247056
67	15 and 66	41567
68	animal/ not human/	1164743
69	nonhuman/	7043049
70	exp Animal Experiment/	2901019
71	exp Experimental Animal/	776639
72	animal model/	1589792
73	exp Rodent/	3873528
74	(rat or rats or mouse or mice).ti.	1563613
75	or/68-74	9201242
76	67 not 75	35048
77	limit 76 to english language	30447
78	climacterium/ or "menopause and climacterium"/	8994
79	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
80	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
81	("change of life" or life change?).tw.	4281
82	or/78-81	184584
83	exp hormone substitution/	61182
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
86	exp *estrogen/	126164
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
89	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
91	or/83-90	401114
92	82 and 91	58995
93	animal/ not human/	1164743
94	nonhuman/	7043049
95	exp Animal Experiment/	2901019
96	exp Experimental Animal/	776639
97	animal model/	1589792

#	Searches	
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242
101	92 not 100	50424
102	limit 101 to english language	43215
103	random*.ti,ab.	1840480
104	factorial*.ti,ab.	44821
105	(crossover* or cross over*).ti,ab.	120165
106	((doubl* or singl*) adj blind*).ti,ab.	261774
107	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1196283
108	crossover procedure/	71600
109	single blind procedure/	47754
110	randomized controlled trial/	730322
111	double blind procedure/	199308
112	or/103-111	2737481
113	CONTROLLED STUDY/	9111478
114	TREATMENT OUTCOME/	935485
115	MAJOR CLINICAL STUDY/	4618747
116	CLINICAL TRIAL/	1046476
117	reviewed.tw.	873307
118	baseline.tw.	1157267
119	(compare$ or compara$).tw.	7021464
120	or/113-119	16140633
121	COHORT ANALYSIS/	901841
122	FOLLOW UP/	1902143
123	LONGITUDINAL STUDY/	179050
124	PROSPECTIVE STUDY/	798586
125	RETROSPECTIVE STUDIES/	1035839
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	1497898
127	(incidence? adj (stud* or research or analys*)).tw.	2924
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	10476
129	(prospective* adj method*).tw.	1417
130	(retrospective* adj design*).tw.	4171
131	case control study/	193429
132	"nested case control".ti,ab.	13700
133	or/121-132	4296161
134	112 or 120 or 133	17894341
135	102 and 134	30379
136	77 or 135	39104
137	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5322870
138	136 not 137	30760

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2 Database: APA PsycInfo <1806 to September Week 4 2022>

3 Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938
4	or/1-3	15066
5	hormone therapy/	2262

#	Searches	
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *estrogens/	5657
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
11	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
12	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
13	or/5-12	24383
14	4 and 13	2373
15	breast neoplasms/	11017
16	Breast/ and exp neoplasms/	300
17	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	15213
18	uterus/ and exp neoplasms/	43
19	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	457
20	ovaries/ and exp neoplasms/	444
21	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	1347
22	((epithelial or germ cell) adj5 ovar*).ti,ab.	58
23	exp dementia/ or exp alzheimer's disease/	87977
24	(amentia* or dementia* or lewy body).ti,ab.	72463
25	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	67104
26	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	120339
27	exp "death and dying"/	45080
28	(death or dying or die* or dead or mortality or fatal*).ti,ab.	218375
29	exp Cardiovascular Disorders/ or Cerebrovascular Accidents/	68930
30	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	14620
31	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	16319
32	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	6390
33	(stroke or strokes).ti,ab,mh.	38668
34	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	14812
35	TIA.ti,ab.	993
36	(myocardial adj2 infarct*).ti,ab.	4538
37	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	1391
38	atrial flutter*.ti,ab.	27
39	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	4960
40	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).mp.	709
41	embolisms/ or thromboses/	1323
42	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	1179
43	osteoporosis/	1165
44	bones/ and (accidents/ or injuries/ or falls/)	117
45	(osteoporo* or osteop?en*).ti,ab.	2275
46	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab,mh.	2050
47	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius	1936

#	Searches	
	or femur* or hip* or lumbar)).ti,ab,mh.	
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *estrogens/	5657
73	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
75	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
76	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
77	or/69-76	24383
78	68 and 77	2373
79	animal.po.	432218
80	(rat or rats or mouse or mice).ti.	123700
81	79 or 80	436853
82	78 not 81	1974
83	limit 82 to english language	1898
84	clinical trial.md.	34832
85	clinical trial.md.	34832
86	Clinical trials/	12104
87	Randomized controlled trials/	913
88	Randomized clinical trials/	383
89	assign*.ti,ab.	106838
90	allocat*.ti,ab.	35101
91	crossover*.ti,ab.	8375
92	cross over*.ti,ab.	3251
93	((doubl* or singl*) adj blind*).ti,ab.	28070
94	factorial*.ti,ab.	21909
95	placebo*.ti,ab.	42984
96	random*.ti,ab.	229145

#	Searches	
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0
101	followup study.md.	86839
102	TREATMENT OUTCOMES/	38539
103	treatment outcome.md.	22898
104	CLINICAL TRIALS/	12104
105	clinical trial.md.	34832
106	reviewed.tw.	93954
107	prospective$.tw.	78083
108	retrospective$.tw.	50502
109	baseline.tw.	133530
110	cohort.tw.	81269
111	case series.tw.	4679
112	(compare$ or compara$).tw.	719207
113	or/100-112	1088229
114	COHORT ANALYSIS/	1643
115	LONGITUDINAL STUDIES/ or longitudinal study.md.	188660
116	FOLLOWUP STUDIES/ or followup study.md.	87168
117	PROSPECTIVE STUDIES/ or prospective study.md.	49600
118	RETROSPECTIVE STUDIES/ or retrospective study.md.	34340
119	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	141639
120	(incidence? adj (stud* or research or analys*)).tw.	614
121	(longitudinal* adj1 (survey* or evaluat*)).tw.	5386
122	(prospective* adj method*).tw.	156
123	(retrospective* adj design*).tw.	489
124	or/114-123	307794
125	99 or 113 or 124	1485971
126	83 and 125	1056
127	64 or 126	1411

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 10 of 12, October 2022

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513

#	Searches	
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56

1

2 Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 10 of 12,
3 October 2022

4 Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56
21	#19 in Trials	8053

5

6 Database: Epistemonikos

7 Date of last search: 27/07/2022

#	Searches	
1	(menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes")	
2	((hormone AND (replac* OR therap* OR substitut*)) OR HRT OR HT OR MHT OR ERT OR EPRT OR SEPRT OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR ((combin* OR sequen* OR continu* OR plus) AND (progest* OR gestagen* OR gestogen* OR medroxyprogesterone* OR norgestrel* OR drospirenone* OR norethisterone* OR dydrogesterone* OR levonorgestrel*)) OR (("body identical*" OR bio-identical* OR bioidentical*) AND hormon*))	
3	1 AND 2	7537

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES	191
9	((hormon* AND (replac* or therap* or substitut*)))	1577
10	((HRT or HT or MHT or ERT or EPRT or SEPRT))	435
11	MeSH DESCRIPTOR Estrogens EXPLODE ALL TREES	136
12	((oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*))	670
13	(((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)))	291
14	((("body identical*" or bio-identical* or bioidentical*) AND hormon*))	3
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2314
16	#7 AND #15	473
17	(#7 AND #15) IN HTA	71

Database: INAHTA

Date of last search: 03/10/2022

#	Searches	
1	"Climacteric"[mh] or "Menopause"[mh] or "Perimenopause"[mh] or "Postmenopause"[mh]	56
2	(menopau* or postmenopau* or perimenopau* or climacteri*)	158
3	("change of life" or "life change" or "life changes")	1
4	#3 OR #2 OR #1	162
5	"Hormone Replacement Therapy"[mhe]	31
6	(hormon* AND (replac* or therap* or substitut*))	161
7	(HRT or HT or MHT or ERT or EPRT or SEPRT)	33
8	"Estrogens"[mhe]	7
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*)	83
10	((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*))	16
11	(("body identical*" or bio-identical* or bioidentical*) AND hormon*)	1
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	232
13	#12 AND #4	73
14	Limit to English Language	57

Economic searches

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352

#	Searches	
55	26 and 54	849

1

2 Database: Embase <1974 to 2022 July 27>

3 Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270
8	letter.pt. or letter/	1241876
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995

#	Searches	
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

1 Database: Cochrane Database of Systematic Reviews (CDSR) Issue 7 of 12, July 2022

2 Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

3

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92

#	Searches	
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN HTA FROM 2012 TO 2022	42

Database: INAHTA

Date of last search: 28/07/2022

#	Searches	
1	"Climacteric"[mh]	2
2	"Menopause"[mh]	28
3	"Perimenopause"[mh]	1
4	"Postmenopause"[mh]	31
5	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
6	("change of life" or "life change" or "life changes")	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	163
8	Limit to English Language	134

Database: EED

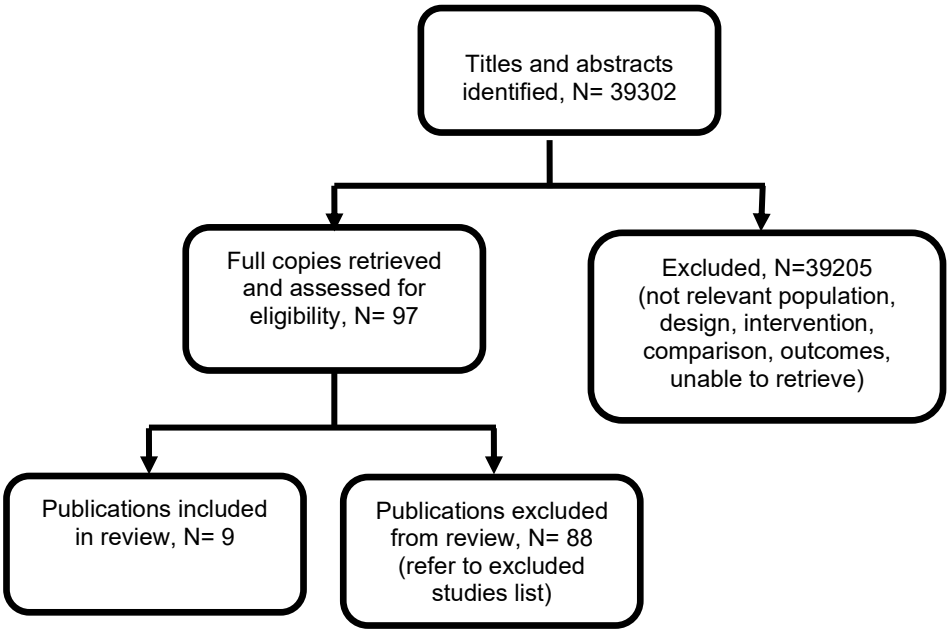
Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN NHSEED FROM 2012 TO 2022	33

Appendix C Effectiveness evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Imtiaz, 2017

Bibliographic Reference Imtiaz, Bushra; Tuppurainen, Marjo; Rikkonen, Toni; Kivipelto, Miia; Soininen, Hilkka; Kroger, Heikki; Tolppanen, Anna-Maija; Postmenopausal hormone therapy and Alzheimer disease: A prospective cohort study.; Neurology; 2017; vol. 88 (no. 11); 1062-1068

Study details

Country/ies where study was carried out	Finland
Study type	Prospective cohort study
Study dates	1999-2009
Inclusion criteria	• Women aged 47–56 years • residents of Kuopio Province, Eastern Finland • had complete data on questionnaire on confounders and self-reported exposure information. A woman was considered postmenopausal if: • 12 or more months had passed since her natural menstrual cycle • had undergone surgical menopause through bilateral oophorectomy with or without hysterectomy • or if the time since menopause and the history of HT use could be clarified from the follow-up questionnaire. Over 90% of women were postmenopausal at the second follow-up.
Exclusion criteria	Not specified
Patient characteristics	**Age at baseline, years - mean (range):** Alzheimer's disease (AD): 54.1 (51.4 to 56.0) No AD: 52 (49.6 to 57.3) (assumed top range as potential error in reporting '47.3') **Average age at Alzheimer's diagnosis, years, mean (range):**

	72.3 years (range 59 to 78.6 years) **Age at menopause, years - mean (range):** AD: 50.4 (45.4 to 54.4) No AD: 51.2 (47.0 to 54.0) **Alcohol use, g/month - mean (range):** AD: 54 (0 to 198) No AD: 68 (0 to 252) **BMI, kg/m2 - mean (range):** AD: 26.4 (23.8 to 28.9) No AD: 26.4 (24.1 to 29.4) **Smoking, yes - number (%):** AD: 72 (25.99) No AD: 1924 (24.30) **Education, number (%):** Compulsory school only (6years): AD: 24 (30.77) No AD: 619 (26.85) Compulsory school and 2 years supplementary school or occupational training: AD: 44 (56.41) No AD: 1338 (58.05) High school and 2 years supplementary school or professional training: AD: 4 (5.13) No AD: 245 (10.63) University degree AD: 6 (7.69) No AD: 103 (4.47) Probable Alzheimer’s Disease diagnosis:

	Based on DSM-IV criteria for AD and National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association. The main diagnostic criteria were progressive decline in memory and cognition and exclusion of other reasons. Diagnosis was supported by abnormal MRI or CSF biomarker findings.
Intervention(s)/control	**Intervention** • Estrogen-only hormone therapy • Combination hormone therapy (estrogen plus progestogen) (continuous or sequential not reported separately therefore classified as any combined in this review) **Control:** No HRT
Duration of follow-up	20 years
Sources of funding	Not industry funded
Sample size	N=8195 Dementia cases, n=490 Control cases, n=7705
Other information	Hazard ratios and 95% confidence intervals were estimated with model adjusted for age, BMI, alcohol, smoking, physical activity, occupation status, number of births, menopause status, any cancer, and surgery. There was no information on apolipoprotein E genotype. Estimates are taken from register-based information on hormone therapy use.

Risk of developing Alzheimer's disease

Outcome	Estrogen-only vs No HRT	Combination HT vs No HRT

Outcome	Estrogen-only vs No HRT	Combination HT vs No HRT
<1 year use Hazard ratio/95% CI	0.85 (0.49 to 1.5)	1.7 (1.1 to 2.6)
1 to 3 years Hazard ratio/95% CI	1.1 (0.66 to 1.8)	1.1 (0.62 to 1.9)
>3 to 5 years Hazard ratio/95% CI	1.1 (0.59 to 1.9)	0.36 (0.11 to 1.1) *(upper CI assumed incorrectly reported)*
>5 to 10 years Hazard ratio/95% CI	0.78 (0.42 to 1.4)	1.4 (0.88 to 2.3)
>10 years Hazard ratio/95% CI	0.26 (0.03 to 1.8)	1.4 (0.64 to 3.3)

1 **Critical appraisal**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Study adjusted for age, BMI, alcohol, smoking, physical activity, occupation status, number of births, menopause status, any cancer, and surgery. No adjustments for predisposing risk factors such as family history or ApoE-4 genotype, and confounding domains adjusted for were self-reported.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Start of follow-up and start of intervention coincide)*
3. Bias in classification of interventions	Risk of bias judgement for classification of	Low *(Classification of the intervention would not have been affected by knowledge of the outcome as the outcome data was collected after intervention was recorded)*

Section	Question	Answer
	interventions	
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(There may be co-interventions but they are not described so no information on whether they are balanced. Participants probably adhered to the intervention, however an issued prescription doesn't necessarily mean the woman took HRT.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Approximately 30% loss of follow-up at 20 years. Participants were excluded if there was no information on exposure, and confounders. Not enough information on analysis to adjust for missing data.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome was assessed using ICD criteria for all participants.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Unlikely that the effect estimate was selected as only one measurement for dementia. No indication other analysis were performed.)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Manson, 2017

Bibliographic Reference Manson, JoAnn E; Aragaki, Aaron K; Rossouw, Jacques E; Anderson, Garnet L; Prentice, Ross L; LaCroix, Andrea Z; Chlebowski, Rowan T; Howard, Barbara V; Thomson, Cynthia A; Margolis, Karen L; Lewis, Cora E; Stefanick, Marcia L; Jackson, Rebecca D; Johnson, Karen C; Martin, Lisa W; Shumaker, Sally A; Espeland, Mark A; Wactawski-Wende, Jean; WHI, Investigators; Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials.; JAMA; 2017; vol. 318 (no. 10); 927-938

Study details

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2014
Inclusion criteria	• Postmenopausal women aged 50 to 79, with or without a uterus • likely to be residing in the area 3 years after randomisation • written consent.
Exclusion criteria	• Any medical condition associated with a survival of less than 3 years • adherence or retention reasons: alcoholism; other drug dependency; mental illness; dementia; active participant in any other interventional trial.
Patient characteristics	**Conjugated equine estrogens (CEE) + medroxyprogesterone (MPA) trial** **Age at screening, years, mean (SD):** Intervention: 63.2 (7.1) Placebo: 63.3 (7.1) **Race ethnicity, number (%):** White Intervention: 7141 (84.0) Placebo: 6805 (84.0) Black Intervention: 548 (6.4) Placebo: 574 (7.1) Hispanic Intervention: 471 (5.5) Placebo: 415 (5.1) American Indian Intervention: 25 (0.3)

	Placebo: 30 (0.4) Asian/Pacific Islander Intervention: 194 (2.3) Placebo: 169 (2.1) Unknown Intervention: 127 (1.5) Placebo: 109 (1.3) **>High school diploma or GED, number (%)** Intervention: 6272 (74.1) Placebo: 5899 (73.3) **Smoking, number (%)** Never Intervention: 4178 (49.6) Placebo: 3999 (50.0) Past Intervention: 3362 (39.9) Placebo: 3157 (39.5) Current Intervention: 880 (10.5) Placebo: 838 (10.5) **CEE only trial** **Age at screening, years, mean (SD):** Intervention: 63.6 (7.3) Placebo: 63.6 (7.3) **Race ethnicity, number (%):** White

	Intervention: 4009 (75.5) Placebo: 4075 (75.1) Black Intervention: 781 (14.7) Placebo: 835 (15.4) Hispanic Intervention: 319 (6.0) Placebo: 332 (6.1) American Indian Intervention: 41 (0.8) Placebo: 34 (0.6) Asian/Pacific Islander Intervention: 86 (1.6) Placebo: 78 (1.4) Unknown Intervention: 74 (1.4) Placebo: 75 (1.4) **>High school diploma or GED, number (%)** Intervention: 3488 (66.3) Placebo: 3678 (68.3) **Smoking, number (%)** Never Intervention: 2723 (51.9) Placebo: 2705 (50.4) Past Intervention: 1986 (37.8)

	Placebo: 2090 (38.9) Current Intervention: 542 (10.3) Placebo: 571 (10.6)
Intervention(s)/control	**Intervention:** • Daily oral CEE (0.625 mg) plus MPA (2.5 mg, Prempro) – oestrogen plus progesterone (continuous combined) • Daily oral CEE (0.625 mg, Premarin) alone – oestrogen-only **Control:** • Placebo
Duration of follow-up	18 years
Sources of funding	Not industry funded
Sample size	**CEE+MPA trial:** N=16608 CEE+MPA: n=8506 Placebo: n=8102 **CEE only trial:** N=10739 CEE only: n=5310 Placebo: n=5429
Other information	Duration of use during the trial: CEE only: 7.2 years median CEE+MPA: 5.6 years median range not reported There was no information on apolipoprotein E genotype.

Alzheimer's or dementia mortality

Outcome	CEE+MPA vs Placebo	CEE vs Placebo
Alzheimer's or dementia mortality - 18 year cumulative follow-up Hazard ratio/95% CI	0.93 (0.77 to 1.11)	0.74 (0.59 to 0.94)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Intention to treat analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Appropriate outcome measures were used with assessors blinded to intervention.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data analysed according to trial protocol.)*
Overall bias and Directness	Risk of bias judgement	Low *(No risk of bias detected.)*
Overall bias and Directness	Overall Directness	Directly applicable

Paganini-Hill, 1996

Bibliographic Reference	Paganini-Hill, A; Henderson, V W; Estrogen replacement therapy and risk of Alzheimer disease.; Archives of internal medicine; 1996; vol. 156 (no. 19); 2213-7

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study (nested case control)
Study dates	1981 to 1995
Inclusion criteria	• Residents who owned homes in Leisure World Laguna Hills (retirement community in Southern California). • Female members of the cohort who had died between 1981 and 1991, and had Alzheimer's Disease diagnosis or other dementia diagnosis mentioned on the death certificate, were included for ascertainment of Alzheimer's disease or other dementia diagnosis.
Exclusion criteria	None specified
Patient characteristics	Postmenopausal women (details not specified) **Age at death, years, mean (SD):** Cases: 87.7 (5.9) Controls: 87.3 (5.5) **Age at last menstrual period, years, number** ≤44 Cases: 59 Controls: 315 45-54 Cases: 142

	Controls: 724 ≥55 Cases: 27 Controls: 120
Intervention(s)/control	**Intervention:** Oral conjugated estrogen therapy (publication includes injection and creams however these are reported combined and therefore only oral estrogen information has been extracted) **Control:** Never used estrogen (not reported if this includes contraceptive pill)
Duration of follow-up	14 years
Sources of funding	Grants from National Cancer Institute; Earl Carroll Trust Fund, Wyeth-Ayerst Laboratories
Sample size	N=3760 female members who had died n=248 women had Alzheimer's disease, senile dementia, dementia, or senility mentioned on the death certificate n= 1240 matched women who did not have the above diseases on the death certificate N=1439 Cases: n=246 Controls: n=1193 Cases and controls do not add up to total individuals due to missing values. Estrogen user: Cases: n=96 Control: n=578 Never user: Cases: n=150 Control: n=615

	Cases of Alzheimer's disease, senile dementia, dementia, or senility were matched to 5 controls without Alzheimer's disease, according to year of death and year of birth (+-1 year).
Other information	Multivariate analysis used to adjust for estrogen use, age at menarche, weight, type of menopause (natural vs surgical), age at last menstrual period, use of blood pressure medication. There was no information on apolipoprotein E genotype.

Outcomes

Risk of dementia: By duration of use

Outcome	**Estrogen user vs No HRT**
<3 years Odds ratio/95% CI	42 cases vs 202 controls 0.83 (0.56 to 1.22)
4 to 14 years use Odds ratio/95% CI	25 cases vs 187 controls 0.5 (0.31 to 0.81)
≥15 years use Odds ratio/95% CI	17 cases vs 159 controls 0.44 (0.26 to 0.75)
Route of administration - oral (conjugated estrogen therapy) for 5 to 14 years duration of use Odds ratio/95% CI	18 cases vs 116 controls 0.61 (0.35 to 1.06)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	**Question**	**Answer**
(A) Are the results of the	1. Did the study address a clearly focused issue?	Yes

Section	Question	Answer
study valid?		
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Can't tell *(The cases were recruited by using death certificates that mentioned an Alzheimer's or other dementia diagnoses. This might not have captured all diagnoses of Alzheimer's or other dementia).*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes *(Controls were matched to cases by year of death and year of birth).*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(The exposure was measured using questionnaires so subject to bias).*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age at menarche; weight; type of menopause; age at last menstrual period, use of blood pressure medication.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	No difference in risk of dementia between users and non-users of estrogen replacement therapy.
(B) What are the results?	8. How precise are the results?	Not precise, confidence intervals are wide.
(B) What are the results?	9. Do you believe the results?	Can't tell *(sample size is small, and there are concerns regarding imprecision and also bias around collection of exposure information as well as cases).*
(C) Will the results help	10. Can the results be applied to the local	No *(Small niche population of residents who owned a home in retirement*

Section	Question	Answer
locally?	population?	*community in California. This population does not represent the wide range of people who take oestrogen replacement therapy in the UK).*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

1 **Paganini-Hill, 2020**

Bibliographic Reference	Paganini-Hill, A; Corrada, M M; Kawas, C H; Prior endogenous and exogenous estrogen and incident dementia in the 10th decade of life: The 90+ Study.; Climacteric : the journal of the International Menopause Society; 2020; vol. 23 (no. 3); 311-315

2

3 **Study details**

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	January 2003 to January 2009
Inclusion criteria	• Members of the Leisure World Cohort Study (see Paganini-Hill 1996) • alive and aged 90 or older on January 1 2003, January 1 2008 and January 1 2009 • no dementia at baseline as ascertained by an in-person evaluation • had at least 1 additional follow-up. Cohort does not overlap with cases in Paganini-Hill 1996 as that publication looked at cases of those who had died.
Exclusion criteria	Non-specified
Patient characteristics	**Age at enrolment for Leisure World Cohort study, years – mean (SD):** Total participants: 68.5 (5) **Age at enrolment for 90+ study, years - mean (SD):** Total participants: 93.2 (2.6)

	Age at last follow-up for 90+ study, years - mean (SD): Total participants: 96.5 (3.2) **Age of diagnosis of dementia, years – mean (SD):** 96.5 (3.1) **Age at last menstrual period, years – number (%):** ≤44: No dementia: 56 (26%) Dementia: 43 (21%) 45-54: No dementia: 125 (59%) Dementia: 137 (66%) 55+: No dementia: 31 (15%) Dementia: 28 (13%) **Dementia** • Neurological examination that involved mental status testing and assessment of functional abilities by a trained physician or nurse practitioner • and a neuropsychological test battery that included the Mini-Mental State Examination.
Intervention(s)/control	**Intervention:** Estrogen replacement therapy (11% of participants used injections or creams - it is unclear whether they are local only, and whether these women also used other systemic estrogens) **Control:** Never users of estrogen replacement therapy
Duration of follow-up	**Mean, years, SD:** 3.4 (2.5)

Sources of funding	Not industry funded
Sample size	N=424 participants Dementia: n=209 No dementia: n=215 Estrogen replacement therapy: n=127 Never users: n=297
Other information	Analysis adjusted for education. There was no information on apolipoprotein E genotype.

Outcomes

Dementia risk by duration of use

Outcome	**Estrogen replacement therapy vs No HRT**
≤3 years use	49 cases vs 39 no dementia
Hazard ratio/95% CI	1.04 (0.71 to 1.53)
4 to 14 year use	62 cases vs 50 no dementia
Hazard ratio/95% CI	1.32 (0.92 to 1.91)
15 years use	39 cases vs 56 no dementia
Hazard ratio/95% CI	0.85 (0.57 to 1.28)

Critical appraisal

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for	Serious *(Study adjusted for confounders, but only education. No adjustments made for*

Section	Question	Answer
	confounding	*other lifestyle factors or predisposing risk factors such as family history or ApoE-4 genotype.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information used to define intervention groups was recorded after the start of the intervention but the outcome was not known.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on cointerventions. HRT use was self-reported, therefore does not necessarily mean they took HRT if they reported they did.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for all participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Knowledge of intervention could not have affected outcome measurement, as the criteria to diagnose dementia was clearly defined.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The results is unlikely to be selected on the basis of multiple outcome measurements or analyses.)*
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

1 **Pourhadi, 2023**

Bibliographic Reference Pourhadi, Nelsan; Mørch, Lina S; Holm, Ellen A; Torp-Pedersen, Christian; Meaidi, Amani; Menopausal hormone therapy and dementia: nationwide, nested case-control study; BMJ; 2023; vol. 381; e072770

2

1 **Study details**

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study – nested case-control
Study dates	Cases and controls identified between 1st January 2000 and 31st December 2018
Inclusion criteria	• Danish women (registered female at birth) • aged 50-60 on 1st January 2000.
Exclusion criteria	• History of dementia, breast cancer, gynaecological cancers, thrombosis, liver disease, thrombophilia, bilateral oophorectomy, and hysterectomy.
Patient characteristics	**Age, mean and SD not reported** **Age, years - median (interquartile range):** Cases of all cause dementia: 70 (66 to 73) Age matched controls without dementia: 70 (66 to 73) **Age at initiation of use, years - median (interquartile range):** *ever users of oestrogen-progestin* Cases of all cause dementia: 53 (50 to 54) Controls: 53 (50 to 54) **Duration of use, - number (%)** Cases of all causes dementia: ≤1 year: 447 (25.1) >1 to 4 years: 460 (25.8) >4 to 8 years: 447 (25.1) >8 to 12 years: 282 (15.8) >12 years: 146 (8.2) Controls: ≤1 year: 4043 (25.0)

	>1 to 4 years: 4397 (27.2) >4 to 8 years: 4468 (27.7) >8 to 12 years: 2311 (14.3) >12 years: 935 (5.8) **Method of treatment - number (%)** Cases of all cause dementia: Continuous progestin: 458 (25.7) Cyclic progestin: 694 (38.9) Continuous and cyclic oestrogen and progestin: 542 (30.4) Unknown: 88 (4.9) Controls: Continuous progestin: 3919 (24.3) Cyclic progestin: 6284 (38.9) Continuous and cyclic oestrogen and progestin: 5096 (31.5) Unknown: 855 (5.3) **Route of administration - number (%):** Cases of all-cause dementia: Oral only: 1609 (90.3) Transdermal only: 56 (3.1) Mixed or other: 117 (6.6) Control: Oral only: 14391 (89.1) Transdermal only: 462 (2.9) Mixed or other: 1301 (8.1) **Active ingredients - number (%):** Cases of all-cause dementia: Oestradiol + norethisterone: 1488 (83.5) Oestradiol + medroxyprogesterone: 525 (29.5) Oestradiol + levonorgestrel: 137 (7.7) Oestradiol + cyproterone: 77 (4.3) Oestradiol + dienogest: 40 (2.2) Controls:

	Oestradiol + norethisterone: 13024 (80.6) Oestradiol + medroxyprogesterone: 5134 (31.8) Oestradiol + levonorgestrel: 1557 (9.6) Oestradiol + cyproterone: 874 (5.4) Oestradiol + dienogest: 270 (1.7) In Denmark, dementia is diagnosed and managed in a hospital setting typically on specialised memory clinics, allowing us to identify a first time diagnosis of dementia from the National Registry of Patients, which holds information on all diagnoses given in Danish hospitals since 1977 for admissions and 1995 for outpatient visitis. Furthermore, drugs used in the treatment of dementia require a prescription, and since 1995, all filled prescriptions are registered in the National Prescription Registry. A woman was considered a case with all cause dementia from the date (index date) of first dementia diagnosis (the 10th revision of the International Classification of Diseases (ICD-10) code F00, F01, F02, F03, G30, G31.8-9) or from the date of redeeming first drug specific to dementia (ie, Anatomical Therapeutic Chemical code N06D). Compared with the control group, the case group had shorter education, lower household income, were more likely to live alone and have hypertension, diabetes, and thyroid disease at time of index. Analysis adjusted for these confounders.
Intervention(s)/control	**Intervention:** • Combined oestrogen and progestin menopausal hormone therapy (continuous combined, cyclic (sequential) combined and any combined) Information about timing, amount, and type (continuous or cyclic) was obtained from the National Prescription Registry from 1 January 1995 until 2 years before index date. **Control:** • Never user of menopausal hormone therapy
Duration of follow-up	18 years
Sources of funding	Not industry funded
Sample size	N=61470 Cases of dementia: 5589 Age matched controls: 55890

Other information	Among all oestrogen-progestin users, 11 879 (66.2%) had their last treatment day more than eight years before the index date, and 1555 (8.7%) were still users at the time of diagnosis or matching. Confounder adjustments: Education, income, cohabitation, hypertension, diabetes, thyroid disease There was no information on apolipoprotein E genotype.

Outcomes

All cause dementia - any combination oestrogen-progestin, past users >8 years since last use

Outcome	HRT use vs No HRT
<1 year use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.21 (1.09 to 1.35)
>1 to 4 years Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.19 (1.07 to 1.33)
>4 to 8 years Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.15 (1.03 to 1.28)
>8 to 12 years Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.39 (1.21 to 1.58)
more than 12 years Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date.	1.74 (1.45 to 2.1)

Outcome	HRT use vs No HRT
Hazard ratio/95% CI	

1 **All cause dementia - continuous oestrogen-progestin, past users, >8 years since last use**

Outcome	HRT use vs No HRT
<1 year use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.22 (1.04 to 1.44)
>1 to 4 years use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.2 (1 to 1.45)
>4 to 8 years Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.44 (1.17 to 1.78)
>8 years use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.99 (1.46 to 2.71)

2 **All cause dementia - cyclic oestrogen-progestin, past users, >8 years since last use**

Outcome	HRT use vs No HRT
< 1 year use (less than or equal to) Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.21 (1.06 to 1.38)

Outcome	HRT use vs No HRT
>1 to 4 years use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.22 (1.06 to 1.41)
>4 to 8 years use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.25 (1.04 to 1.51)
>8 years use Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Hazard ratio/95% CI	1.59 (1.09 to 2.31)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results	5. Was the exposure accurately measured to	Yes

Section	Question	Answer
of the study valid?	minimise bias?	
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Can't tell *(BMI, ApoE-4 genotype, lifestyle factors (smoking or alcohol intake) cholesterol levels and socioeconomic status have not been adjusted for.)*
(B) What are the results?	7. What are the results of this study?	The risk of all cause dementia is increased with HRT use, and increases with longer durations of use
(B) What are the results?	8. How precise are the results?	Precise
(B) What are the results?	9. Do you believe the results?	Yes to a degree - some confounders have not been adjusted for.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(The results fit some evidence but not all as there is contradictory evidence which shows no difference in risk of all cause dementia with HRT use.)*

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2 **Seshadri, 2001**

Bibliographic Reference	Seshadri, S; Zornberg, G L; Derby, L E; Myers, M W; Jick, H; Drachman, D A; Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease.; Archives of neurology; 2001; vol. 58 (no. 3); 435-40

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study (nested case-control)
Study dates	January 1991 - October 1998
Inclusion criteria	• Women born on or before January 1 1950. • Having received at least one prescription for a systemic estrogen preparation between January 1990 - October 1998. • Current users of estrogen replacement therapy, defined as a prescription in the last year.
Exclusion criteria	Any diagnosis of: • alcoholism or other drug addiction • psychotic disorder • Parkinson's disease • stroke • motor neuron disease • deep vein thrombosis • pulmonary emboli • cancer
Patient characteristics	**Age – mean, years:** Cases: 66.7 Control: 65.2 SD not reported **Estrogen exposure – mean, years**: Cases: 4.2 Control: 4.5 **BMI, number:**

	<23kg/m2: Cases: 13 Control: 38 23-26.9kg/m2: Cases: 18 Control: 64 >27kg/m2: Cases: 5 Control: 55 Unknown: Cases: 23 Control: 64 **Cigarette smoking status, number:** Nonsmoker: Cases: 35 Control: 131 Current smoker: Cases: 10 Control: 32 Ex-smoker: Cases: 3 Control: 29 Unknown: Cases: 11 Control: 29 **Diagnosis of dementia:**

	Based on the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related disorders Associations (NINCDS-ADRDA) criteria for probable dementia. • Evidence of dementia required: define as impairment of memory with deficits in at least 2 other domains of cognitive function. • Diagnosis was concurred between reviewing neurologists and the consulting specialist (neurologist, psychiatrist, or consultant geriatrician).
Intervention(s)/control	**Intervention:** Current users of hormone replacement therapy: Estrogen with progestins (continuous or sequential not reported separately therefore classified as any combined in the review) Estrogen-only **Control:** No HRT
Duration of follow-up	Average (if mean, mode or median not reported), range: 5.34 years, range (2.04 to 7.79)
Sources of funding	National Institute of Aging; National Institute of Health; AstraZeneca; Janssen Pharmaceutical; Johnson Pharmaceutical
Sample size	N= 280 Cases: n=59 Controls: n=221
Other information	Relative risks are adjusted for smoking and body mass index. There was no information on apolipoprotein E genotype.

Outcomes

Outcomes

Outcome	Estrogen-only vs No HRT	Estrogen + Progestin vs No HRT
AD incidence - current users, unknown duration of use Relative risk/95% CI	0.89 (0.35 to 2.3)	1.45 (0.6 to 3.49)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes *(Cases were located from the General Practice Research Database, which is a large database covering around 300 general practices in the UK.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes *(Controls were matched to the cases on age within 5 years, physician's practice, index date, and date of first prescription in the database.*)
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Exposure information was taken from prescription information on the databases, however prescription issued does not necessarily mean that the woman took the prescription.)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	BMI; educational level
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes *(Author adjusted analysis for BMI and educational level.)*

Section	Question	Answer
(B) What are the results?	7. What are the results of this study?	No difference between users of hormone replacement therapy and non users on the risk of Alzheimer's disease.
(B) What are the results?	8. How precise are the results?	Not precise as confidence intervals are wide.
(B) What are the results?	9. Do you believe the results?	Can't tell due to wide confidence intervals and small sample size.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes *(The population studied is a UK population.)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

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2 **Shumaker 2003 and 2004**

Bibliographic Reference

Shumaker, Sally A; Legault, Claudine; Rapp, Stephen R; Thal, Leon; Wallace, Robert B; Ockene, Judith K; Hendrix, Susan L; Jones, Beverly N 3rd; Assaf, Annlouise R; Jackson, Rebecca D; Kotchen, Jane Morley; Wassertheil-Smoller, Sylvia; Wactawski-Wende, Jean; 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; vol. 289 (no. 20); 2651-62

Shumaker, Sally A; Legault, Claudine; Kuller, Lewis; Rapp, Stephen R; Thal, Leon; Lane, Dorothy S; Fillit, Howard; Stefanick, Marcia L; Hendrix, Susan L; Lewis, Cora E; Masaki, Kamal; Coker, Laura H; 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; vol. 291 (no. 24); 2947-58

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4 **Study details**

Country/ies where study was carried out	USA

Study type	Randomised controlled trial; WHIMS (sub-trial from WHI)
Study dates	June 1995 - July 2002 for Estrogen + Progestin June 1995 - January 2004 for Estrogen-only
Inclusion criteria	• 65 years to 79 years of age • Free of probable dementia
Exclusion criteria	• Invasive cancer in past 10 years • Breast cancer at any time or suspicion of breast cancer at baseline screening • Acute myocardial infarction, stroke, or transient ischemic attack in the previous 6 months • Known chronic active hepatitis • Safety or adherence or retention concerns
Patient characteristics	**Estrogen + Progestin Trial** **Age- Number (%) – years** 65-69: Combined HRT: 1040 (46.7) Placebo: 1081 (46.9) 70-74: Combined HRT: 779 (35) Placebo: 829 (36) >75: Combined HRT: 410 (18.4) Placebo: 393 (17.1) **Education - Number (%)** < High school: Combined HRT: 150 (6.7) Placebo: 148 (6.5)

	High school/ GED: Combined HRT: 446 (20) Placebo: 498 (21.7) < 4 years College: Combined HRT: 894 (40.2) Placebo: 870 (37.9) > 4 years College: Combined HRT: 734 (33) Placebo: 779 (33.9) **Smoking status - Number (%):** Never: Combined HRT: 1176 (52.8) Placebo: 1172 (51.9) Previous: Combined HRT: 876 (39.8) Placebo: 930 (41.1) Current: Combined HRT: 149 (6.7) Placebo: 158 (6.9) **Prior hormone therapy use - Number (%):** Any: Combined HRT: 485 (21.8) Placebo: 516 (22.4) Estrogen-only: Combined HRT: 305 (13.7) Placebo: 323 (14.0) Estrogen and progestin:

	Combined HRT: 222 (10) Placebo: 236 (10.3) **Estrogen-only trial** **Age- Number (%) – years** 65-69: Estrogen-only: 646 (44.1) Placebo: 667 (45) 70-74: Estrogen-only: 559 (38.2) Placebo: 511 (34.5) >75: Estrogen-only: 259 (17.7) Placebo: 305 (20.6) **Education - Number (%)** < High school: Estrogen-only: 143 (9.8) Placebo: 133 (9.0) High school/ GED: Estrogen-only: 349 (23.9) Placebo: 352 (23.8) < 4 years College: Estrogen-only: 629 (43.1) Placebo: 609 (41.2) > 4 years College: Estrogen-only: 337 (23.1) Placebo: 383 (25.9)

	Smoking status - Number (%): Never: Estrogen-only: 789 (54.5) Placebo: 770 (52.8) Previous: Estrogen-only: 553 (38.2) Placebo: 571 (39.2) Current: Estrogen-only: 105 (7.3) Placebo: 105 (7.3) **Prior hormone therapy use - Number (%):** Any: Estrogen-only: 670 (45.8) Placebo: 670 (45.8) Estrogen-only: Estrogen-only: 654 (44.7) Placebo: 654 (44.7) Estrogen and progestin: Estrogen-only: 42 (2.9) Placebo: 33 (2.2) **Estrogen + Progestin or Estrogen Alone** **Age, number (%):** Estrogen + Progestin or Estrogen Alone: 65-69: 1680 (45.5) 70-74: 1336 (36.2) ≥75: 676 (18.3)

	Placebos: 65-69: 1735 (45.8) 70-74: 1342 (35.5) ≥75: 709 (18.7) **Diagnosis of dementia:** Participants were evaluated by a physician (geriatrician, neurology, or geriatric psychiatrist) who was identified as having the experience required to diagnose dementia. Diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. If the clinician suspected probable dementia, the participants was referred for computed tomography scan and blood tests to rule out reversible causes of dementia.
Intervention(s)/control	**Intervention** Estrogen + Progestin (continuous combined): 1 daily tablet containing conjugated equine estrogen (0.625 mg) and medroxyprogestorone acetate (2.5mg) Estrogen-only: 1 daily tablet containing conjugate equine estrogen (0.625mg) **Control** Matching placebo
Duration of follow-up	Estrogen and progestin, years, mean (SD): 4.01 (1.21) Placebo, years, mean (SD): 4.06 (1.18) Estrogen alone, years, mean (SD): 5.16 (1.77) Placebo, years, mean (SD): 5.20 (1.71)

Sources of funding	Wyeth Pharmaceuticals National Heart Blood and Lung Institute of the National Institutes of Health (US department of Health and Human Services)
Sample size	**Estrogen + Progestin Trial** N= 4532 Intervention: n= 2229 Control: n= 2303 **Estrogen-only trial** N=2946 Intervention: n= 1464 Control: n=1483
Other information	There was no information on apolipoprotein E genotype.

Outcomes

Outcome

Outcome	**Estrogen-only, N = 1464**	**Placebo to estrogen-only, N = 1483**	**Estrogen + Progestin, N = 2229**	**Placebo to estrogen + progestin, N = 2303**
Probable dementia No of events	n = 28	n = 19	n = 40	n = 21

Critical appraisal

Section	**Question**	**Answer**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with intention to treat analysis used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Intention to treat analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Appropriate measures were used.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data analysed according to trial protocol.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

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2 **Vinogradova, 2021**

Bibliographic Reference	Vinogradova, Yana; Dening, Tom; Hippisley-Cox, Julia; Taylor, Lauren; Moore, Michael; Coupland, Carol; Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases.; BMJ (Clinical research ed.); 2021; vol. 374; n2182

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4 **Study details**

Country/ies where	UK

study was carried out	
Study type	Retrospective cohort study (nested case-control)
Study dates	January 1998 - July 2020
Inclusion criteria	• Women aged over 55 and registered in QResearch database or Clinical Practice Research Database GOLD between 1 January 1998 and 31 July 2020.
Exclusion criteria	• Recorded dementia, or dementia related prescriptions before entry into study.
Patient characteristics	**Age, years - Mean (SD):** QResearch • Cases: 83.8 (6.6) • Control: 83.5 (6.3) CPRD • Cases: 83.0 (7.5) • Control: 82.6 (7.3) **Mean (SD) years of records:** QResearch • Cases: 16.5 (4.4) • Control: 16.5 (4.4) CPRD • Cases: 14.9 (4.1) • Control: 15.4 (4.3)

	Body Mass Index (kg/m2), mean (SD) QResearch • Cases: 26.7 (4.9) • Control: 26.9 (4.8) CPRD • Cases: 27.2 (4.9) • Control: 27.3 (4.8) **Diagnosis of dementia:** Dementia diagnoses were taken from general practice records, hospital episode statistics and mortality data. Dementia diagnosed in secondary care memory clinics staffed by specialists, or in general practices using computed tomography and supported by specialists.
Intervention(s)/control	**Intervention** • Estrogen-only hormone therapy • Combination hormone therapy (continuous or sequential not reported separately therefore classified as any combined in the review) **Control:** None users
Duration of follow-up	• 10 years
Sources of funding	• National Institute for Health Research (NIHR) School for Primary Care Research (Nottingham University and Oxford University)
Sample size	N=615917 Cases: n= 118501 Controls: n=497416

	• Qresearch Cases: n= 68738 Control: n= 267490 • CPRD: Cases: n= 49763 Control: n= 229926 Cases were matched to controls by age, general practice and index date.
Other information	Odds ratios are adjusted for smoking, alcohol consumption, Townsend deprivation score (QResearch only), body mass index, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other drugs, and years of data. Prescription in the 3 years before index date were not included in the study's main analysis to minimise protopathic bias. There was no information on apolipoprotein E genotype.

Outcomes

Risk of dementia

Outcome	**Estrogen-only vs No HRT**	**Estrogen + Progestin vs No HRT**
Years of use		
< 1 year Odds ratio/95% CI	1.05 (0.99 to 1.12)	1.01 (0.97 to 1.06)
1 to 3 years	1 (0.93 to 1.07)	0.98 (0.97 to 1.03)

Outcome	Estrogen-only vs No HRT	Estrogen + Progestin vs No HRT
Odds ratio/95% CI		
3 to 5 years Odds ratio/95% CI	0.92 (0.85 to 1)	0.97 (0.92 to 1.03)
5 to <10 years Odds ratio/95% CI	0.99 (0.94 to 1.05)	1 (0.95 to 1.05)
> 10 years Odds ratio/95% CI	0.93 (0.86 to 1)	1.05 (0.97 to 1.13)
Progestogenic constituent		
Medroxyprogesterone (for ≥5 years use) Odds ratio/95% CI	NA	1.01 (0.92 to 1.12)
Levonorgestrel (for ≥5 years use) Odds ratio/95% CI	NA	1.04 (0.97 to 1.11)
Norethisterone (for ≥5 years use) Odds ratio/95% CI	NA	1 (0.94 to 1.07)
Dydrogesterone (1 to 11 years use) Odds ratio/95% CI	NA	0.88 (0.75 to 1.02)
Type of estrogen		
Conjugated equine estrogen (≥ 5 years) Odds ratio/95% CI	0.97 (0.91 to 1.04)	NA

Outcome	Estrogen-only vs No HRT	Estrogen + Progestin vs No HRT
Estradiol (for ≥5 years use) Odds ratio/95% CI	0.98 (0.91 to 1.04)	NA
Mode of administration Estrogen alone, OR estrogen combined with norethisterone		
Oral (5 to <10 years) Odds ratio/95% CI	0.89 (0.72 to 1.09)	0.96 (0.79 to 1.15)
Transdermal 5 to <10 years for Estrogen-only; 5 years or more for combined Odds ratio/95% CI	0.91 (0.79 to 1.03)	1.04 (0.96 to 1.13)
Age at first use <60 (for 5-9 years duration) Odds ratio/95% CI	1.02 (0.94 to 1.1)	1.01 (0.95 to 1.07)
Age at first use 60 or older (for 5-9 years duration) Odds ratio/95% CI	0.97 (0.9 to 1.05)	0.98 (0.91 to 1.06)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes *(Cases were ascertained using dementia diagnosis in general practice records.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes *(Controls were matched using incidence density sampling by year of birth up to 5 controls. Women were matched from the same practice on index date.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Information on exposure is taken from prescription records, however an issued prescription does not necessarily mean the woman took the HRT.)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Smoking, alcohol consumption, Townsend deprivation (QResearch only), body mass index, ethnicity, family history of dementia, oophorectomy/hysterectomy, records of menopause, comorbidities, other drugs, and years of data.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes *(Analyses were adjusted for confounders.)*
(B) What are the results?	7. What are the results of this study?	Overall there were no associations between HRT use and risk of developing dementia.
(B) What are the results?	8. How precise are the results?	Precise, the sample size is large.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes *(UK databases are used.)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

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Appendix E Forest plots

Forest plots for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in Appendix F.

1 ***Comparison 1: Oestrogen plus progestogen, any combined, versus no HRT***

Figure 2: Risk of dementia: unknown recency, by duration of use (results reported as hazard ratios)

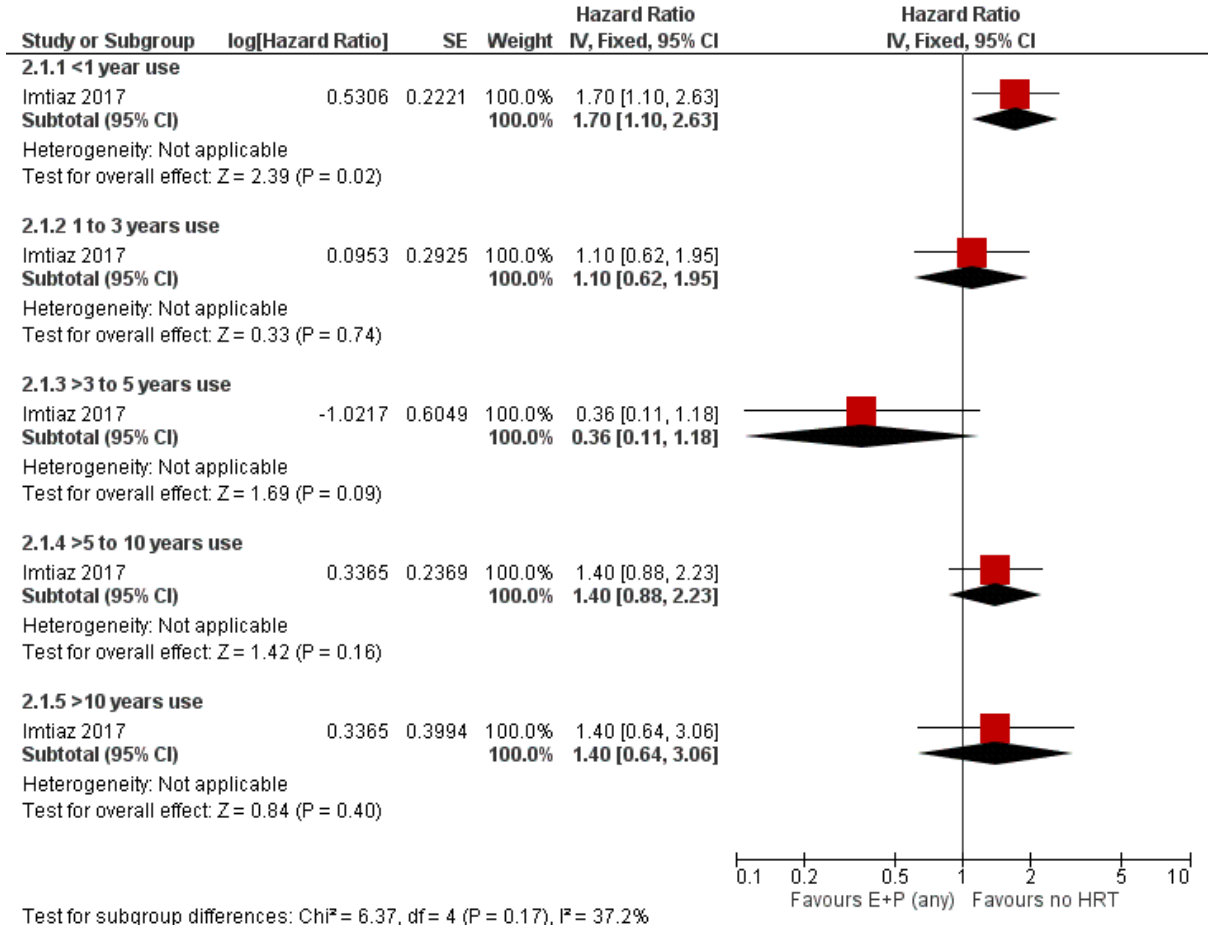


Figure 3: Risk of dementia: unknown recency, by duration of use (results reported as odds ratios)

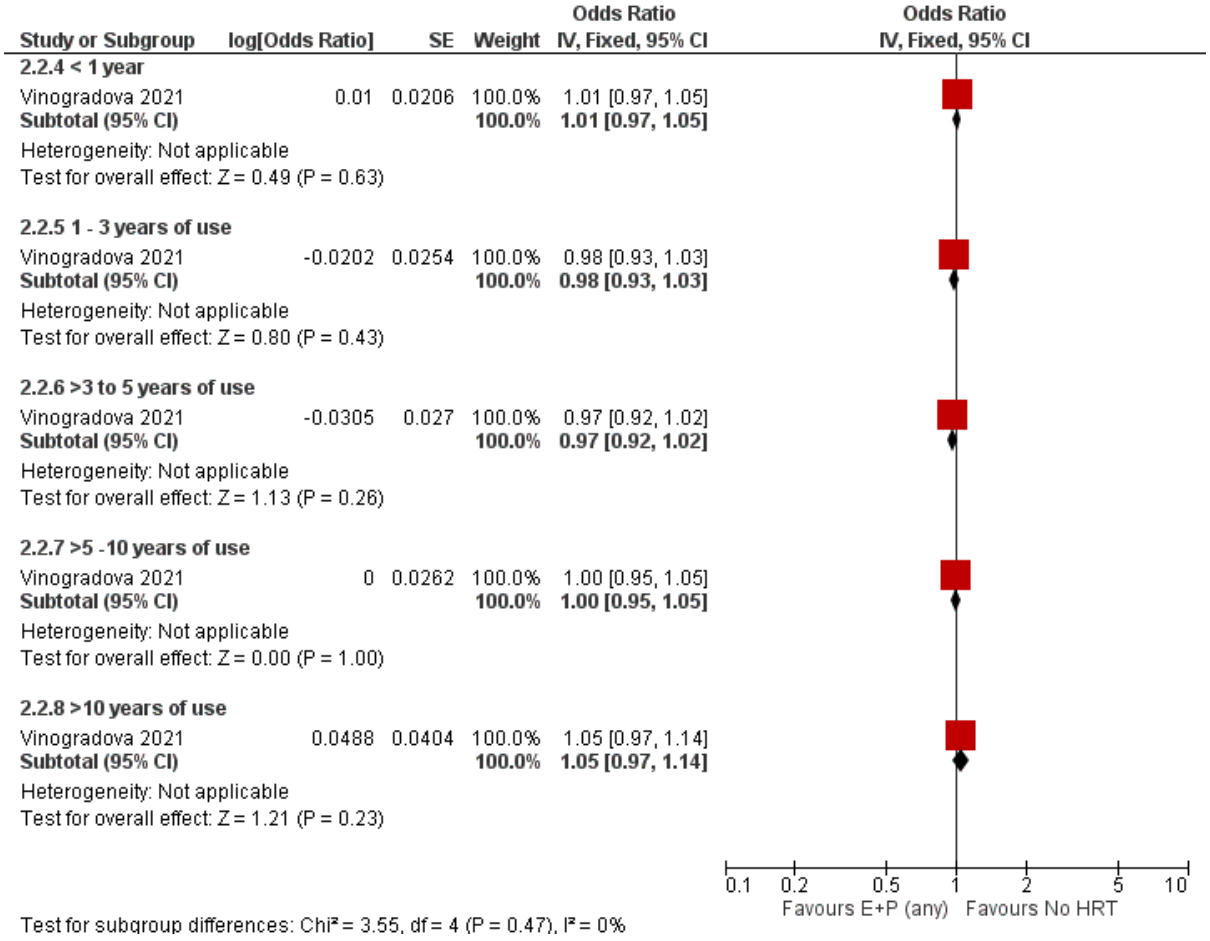


Figure 4: Risk of dementia: past users, >8 years since last use, by duration of use

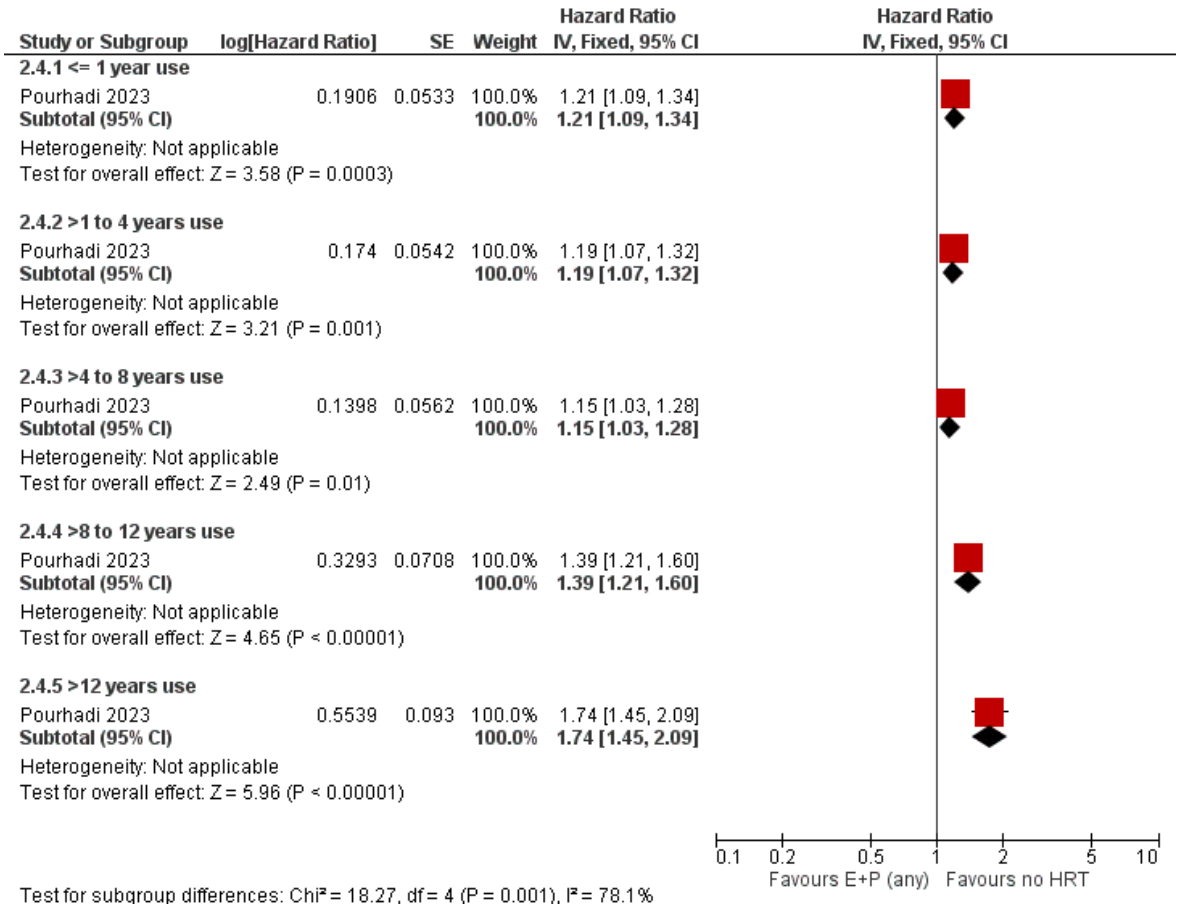


Figure 5: Risk of dementia: by progestogenic constituent, unknown recency, for 5 or more years use

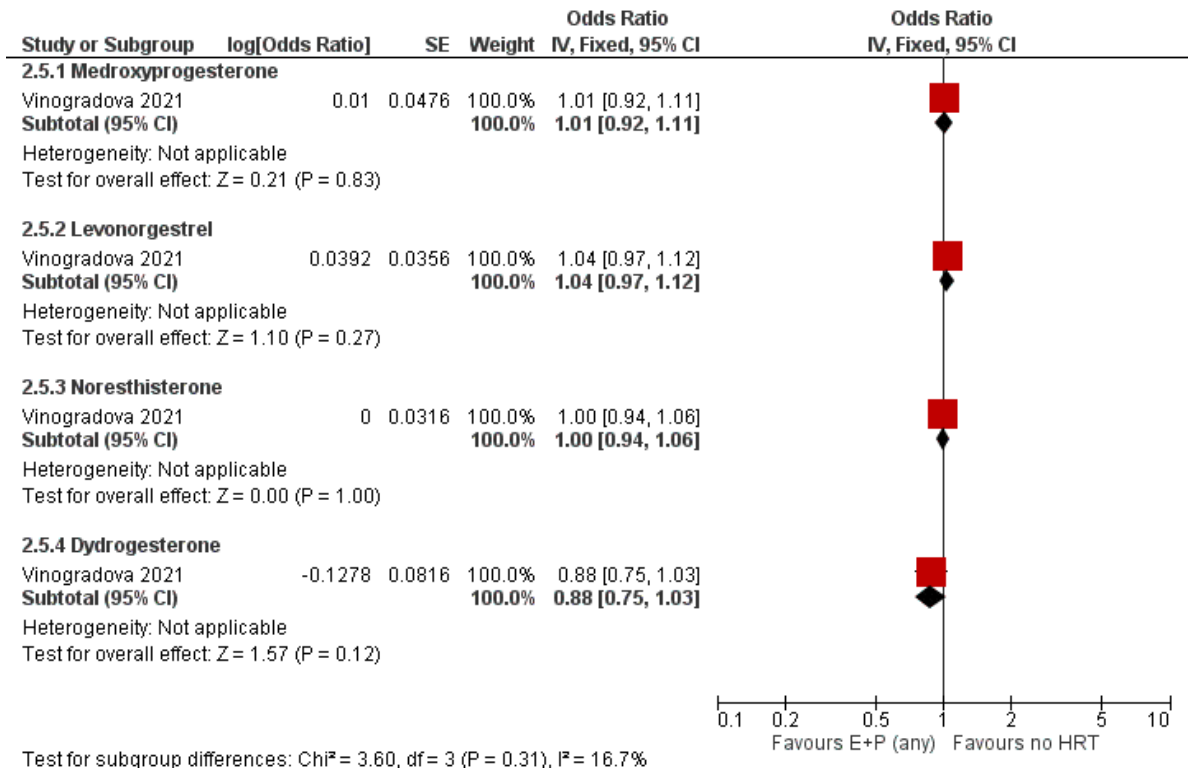

Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio IV, Fixed, 95% CI
Odds Ratio IV, Fixed, 95% CI
2.5.1 Medroxyprogesterone
Vinogradova 2021 0.01 0.0476 100.0% 1.01 [0.92, 1.11]
Subtotal (95% CI) 100.0% 1.01 [0.92, 1.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)
2.5.2 Levonorgestrel
Vinogradova 2021 0.0392 0.0356 100.0% 1.04 [0.97, 1.12]
Subtotal (95% CI) 100.0% 1.04 [0.97, 1.12]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
2.5.3 Noresthisterone
Vinogradova 2021 0 0.0316 100.0% 1.00 [0.94, 1.06]
Subtotal (95% CI) 100.0% 1.00 [0.94, 1.06]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
2.5.4 Dydrogesterone
Vinogradova 2021 -0.1278 0.0816 100.0% 0.88 [0.75, 1.03]
Subtotal (95% CI) 100.0% 0.88 [0.75, 1.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
0.1
0.2
0.5
1
2
5
10
Favours E+P (any)
Favours no HRT
Test for subgroup differences: Chi² = 3.60, df = 3 (P = 0.31), I² = 16.7%

Figure 6: Risk of dementia: by mode of administration (for combined with norethisterone), unknown recency, for 5 to 14 years use

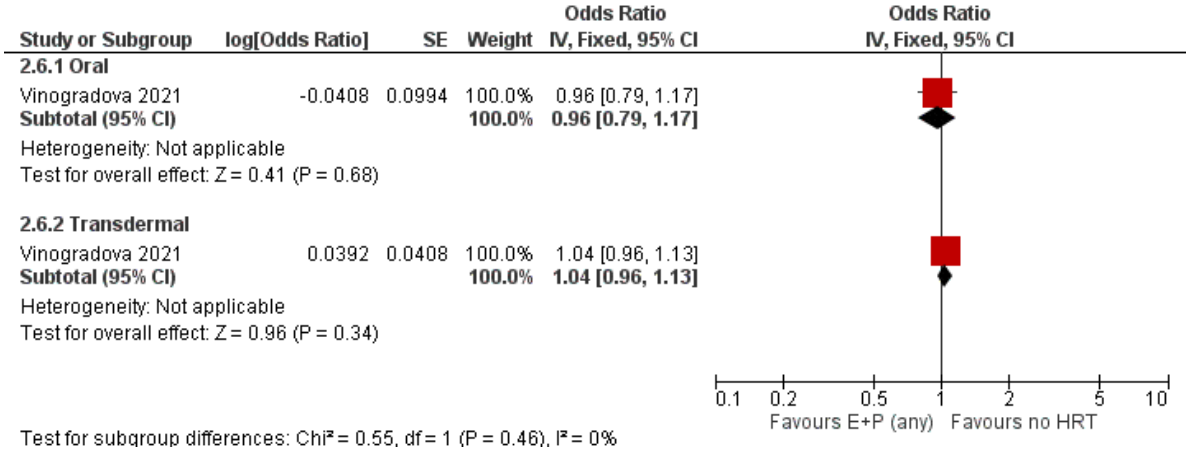
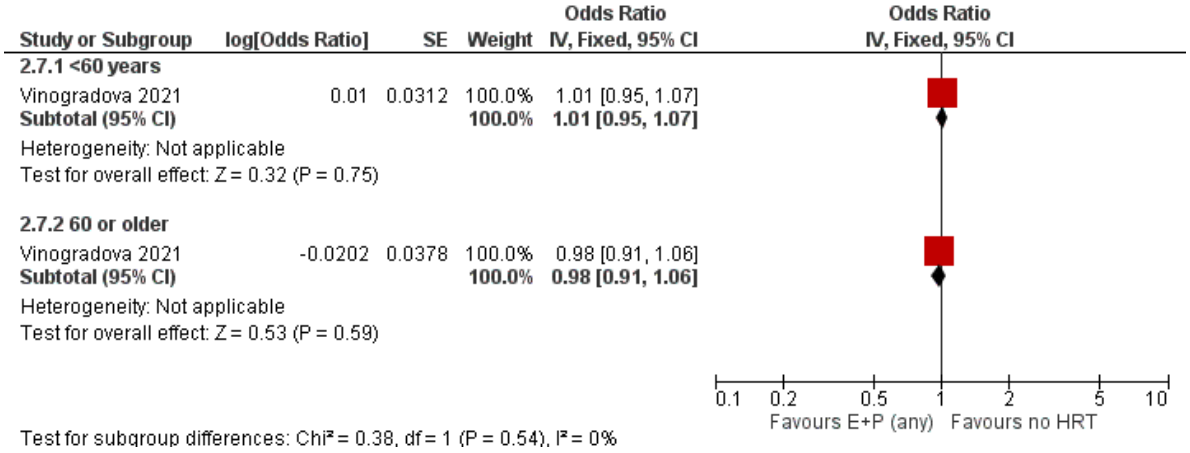
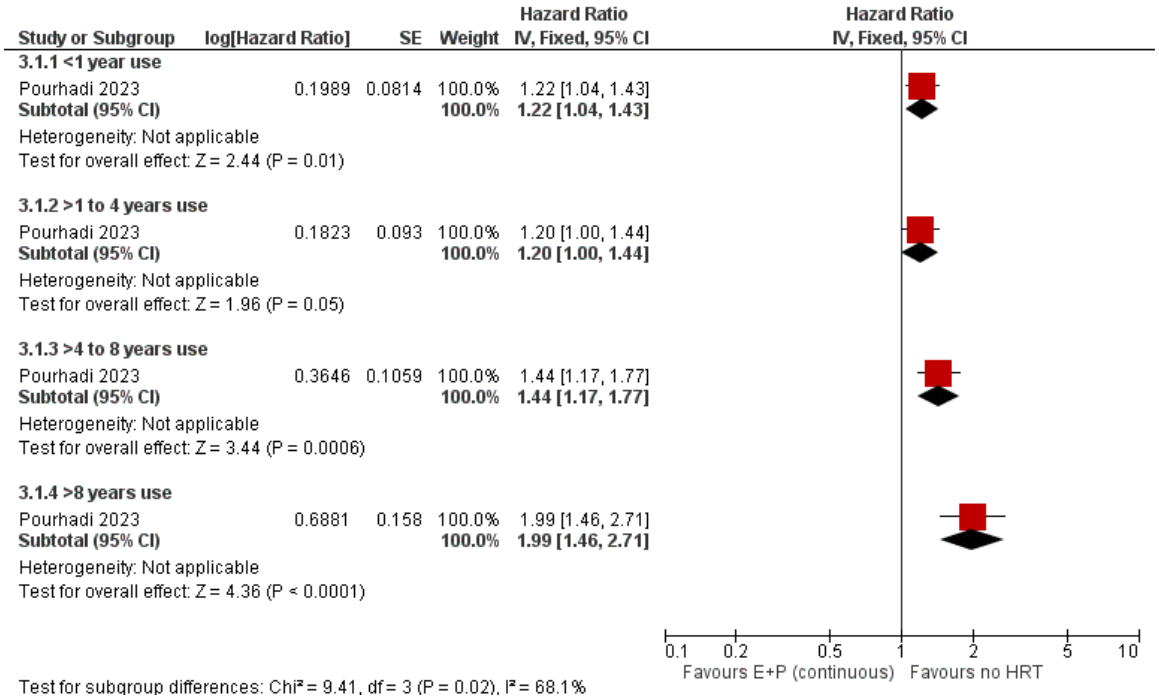


Figure 7: Risk of dementia: by age at first use, for 5 to 9 years use



Comparison 2: Oestrogen plus progestogen, continuous combined, versus no HRT

Figure 8: Risk of dementia: past users, >8 years since last use, by duration of use



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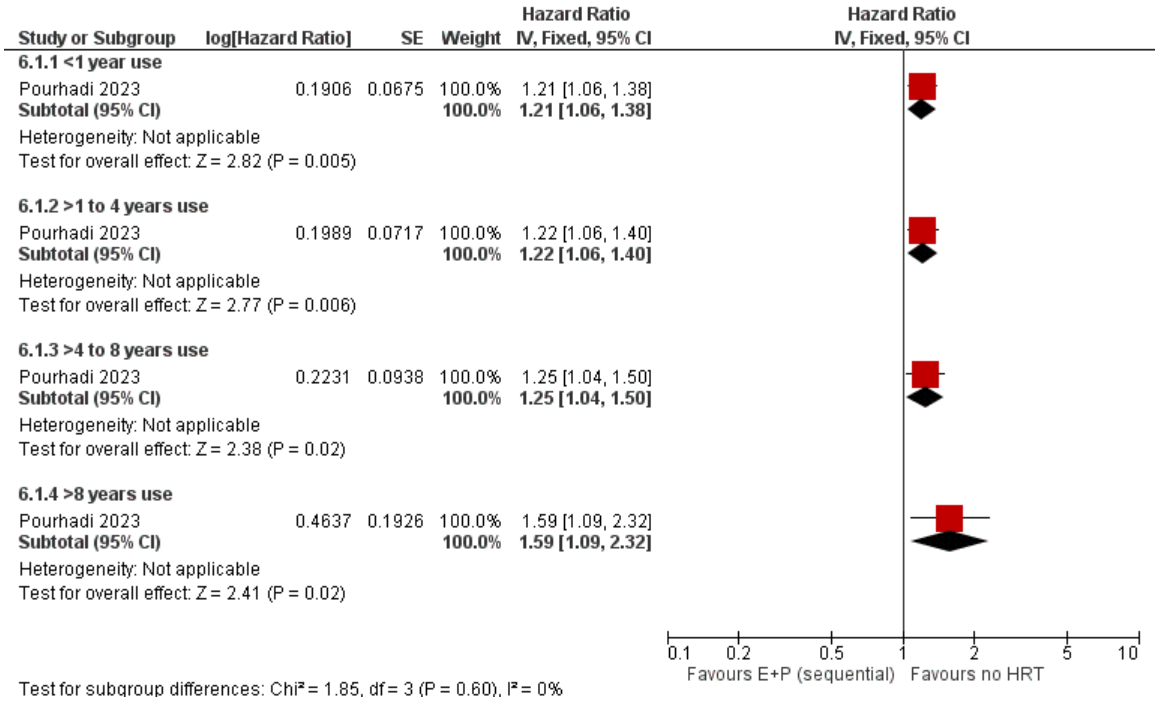
Comparison 3: Oestrogen plus progestogen, sequential combined, versus no HRT

Figure 9: Risk of dementia: past users, >8 years since last use, by duration of use



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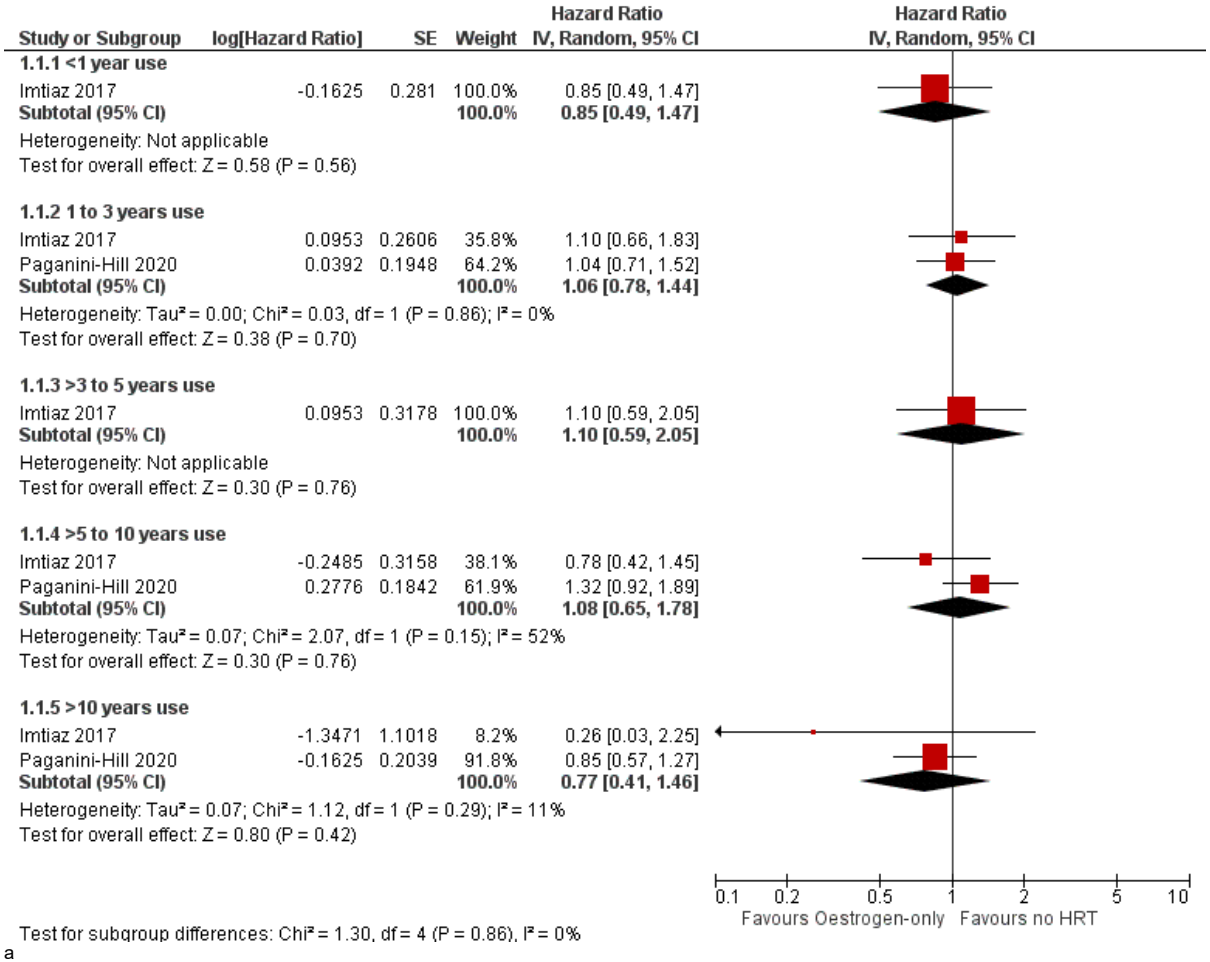
1 ***Comparison 5: Oestrogen-only versus no HRT***

Figure 10: Risk of dementia: unknown recency, by duration of use (results reported as hazard ratios)



[a]

[a] For presentational purposes, this forest plot includes a random effects model due to I^2 = 52% for subgroup >5 to 10 years. However, for subgroup >10 years, which has low heterogeneity (I^2 = 11%), the correct model to use would be a fixed effect and when that is used the pooled HR is 0.82 (0.55 to 1.21).

Figure 11: Risk of dementia: unknown recency, by duration of use (results reported as odds ratios)

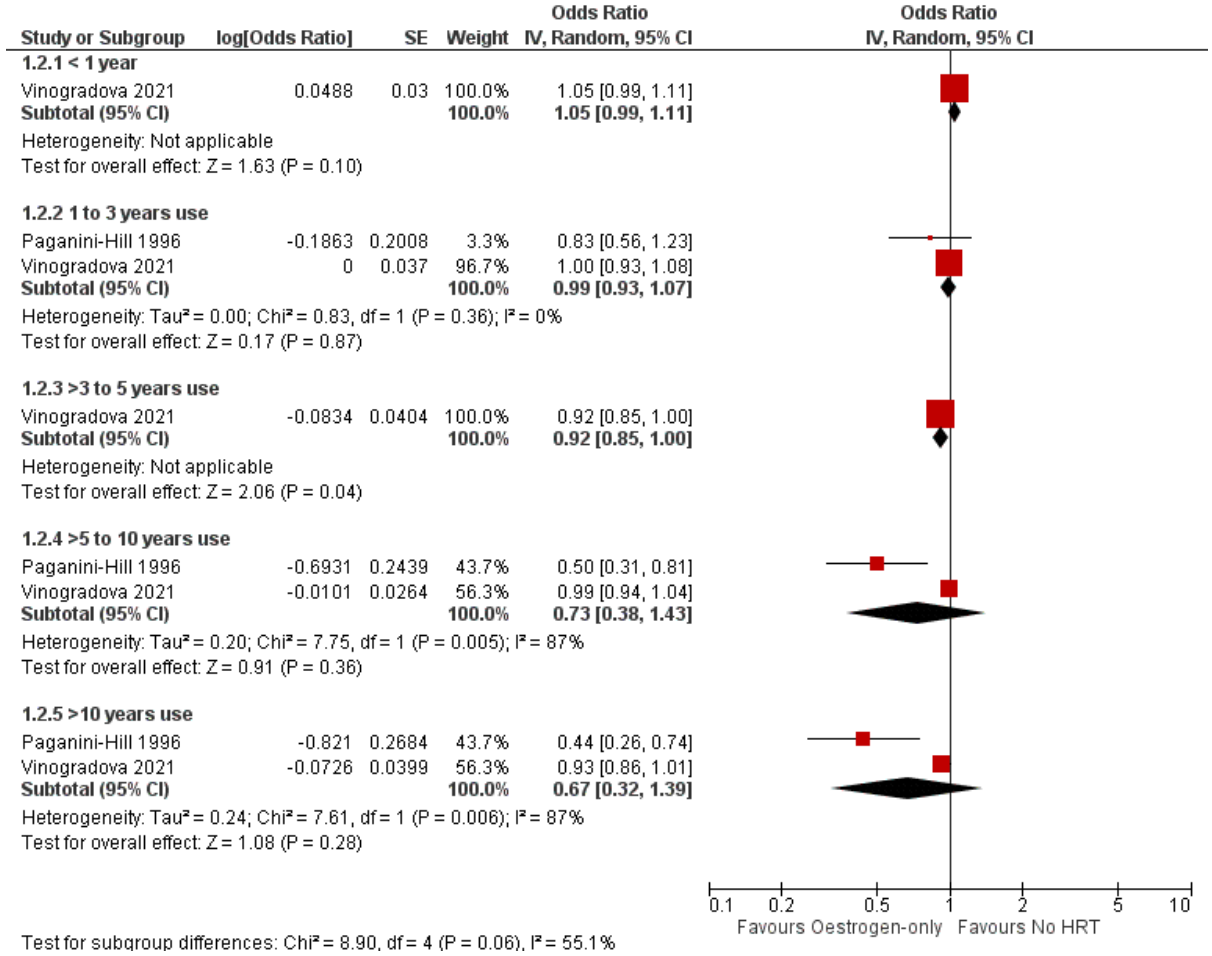


Figure 12: Risk of dementia: by constituent, unknown recency, for 5 or more years use

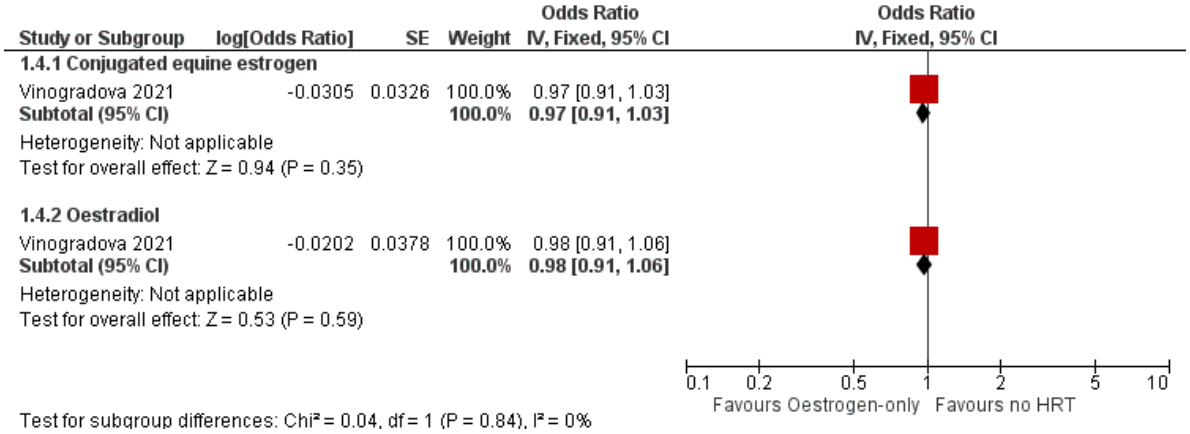


Figure 13: Risk of dementia: by mode of administration, unknown recency, for 5 or more years use

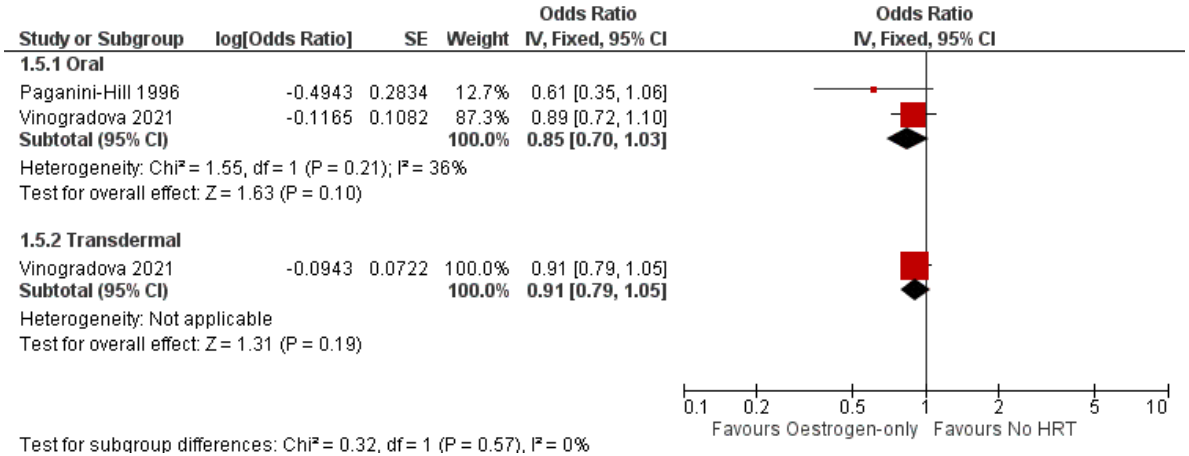
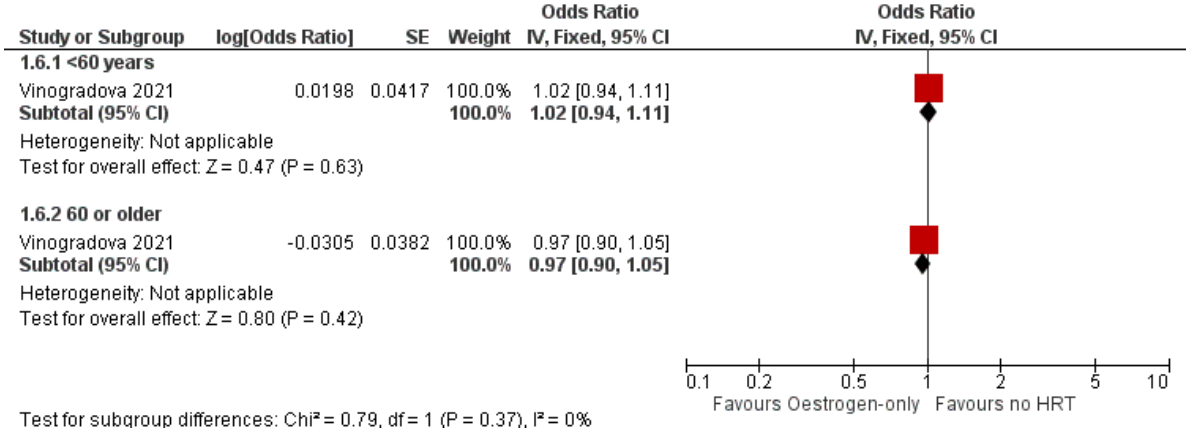


Figure 14: Risk of dementia: by age at first use, for 5 to 9 years use



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Appendix F GRADE tables

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia

Table 4: Comparison 1: Oestrogen plus progestogen, any combined, versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	no HRT	Relative (95% CI)	Absolute		
Dementia, unknown recency by duration of use: <1 year use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	NR[3]	147/4153 (3.5%)	HR 1.7 (1.1 to 2.63)	Not calculable	LOW	CRITICAL
Dementia, unknown recency by duration of use: < 1 year use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3118 cases 13240 controls	3.5%[4]	OR 1.01 (0.97 to 1.05)	0 more per 1000 (from 1 fewer to 2 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: 1 to 3 years use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	NR[3]	147/4153 (3.5%)	HR 1.1 (0.62 to 1.95)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration use: 1 to 3 years use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2101 cases 9191 controls	3.5%[4]	OR 0.98 (0.93 to 1.03)	1 fewer per 1000 (from 2 fewer to 1 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >3 to 5 years use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	no HRT	Relative (95% CI)	Absolute		
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	NR[3]	147/4154 (3.5%)	HR 0.36 (0.11 to 1.18)	Not calculable	LOW	CRITICAL
Dementia, unknown recency by duration of use: >3 to 5 years of use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1513 cases 6641 controls	3.5%[4]	OR 0.97 (0.92 to 1.02)	1 fewer per 1000 (from 3 fewer to 1 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >5 to 10 years use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	NR[3]	147/4154 (3.5%)	HR 1.4 (0.88 to 2.23)	Not calculable	LOW	CRITICAL
Dementia, unknown recency by duration of use: >5 to 10 years of use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2445 cases 10404 controls	3.5%[4]	OR 1 (0.95 to 1.05)	0 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >10 years use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	NR[3]	147/4154 (3.5%)	HR 1.4 (0.64 to 3.06)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration use: >10 years use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	925 cases 3698 controls	3.5%[4]	OR 1.05 (0.97 to 1.14)	2 more per 1000 (from 1 fewer to 5 more)	VERY LOW	CRITICAL
Dementia, current users unknown duration of use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	no HRT	Relative (95% CI)	Absolute		
Seshadri 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	9 cases 27 controls	3.5%[4]	OR 1.45 (0.6 to 3.5)	15 more per 1000 (from 14 fewer to 78 more)	VERY LOW	CRITICAL
Dementia, past users, >8 years since last use, by duration of use - ≤ 1 year use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	447 cases 4043 controls	3.5%[4]	HR 1.21 (1.09 to 1.34)	Not calculable	VERY LOW	CRITICAL
Dementia, past users, >8 years since last use, by duration of use, >1 to 4 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	460 cases 4397 controls	3.5%[4]	HR 1.19 (1.07 to 1.32)	Not calculable	VERY LOW	CRITICAL
Dementia, past users, >8 years since last use, by duration of use, >4 to 8 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	447 cases 4468 controls	3.5%[4]	HR 1.15 (1.03 to 1.28)	Not calculable	VERY LOW	CRITICAL
Dementia, past users, >8 years since last use, by duration of use, >8 to 12 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	282 cases 2311 controls	3.5%[4]	HR 1.39 (1.21 to 1.6)	Not calculable	VERY LOW	CRITICAL
Dementia, past users, >8 years since last use, by duration of use, >12 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	146 cases 935 controls	3.5%[4]	HR 1.74 (1.45 to 2.09)	Not calculable	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	no HRT	Relative (95% CI)	Absolute		
Dementia - by progestogenic constituent, unknown recency, for 5 or more years use – Levonorgestrel												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1250 cases 5159 controls	3.5%[4]	OR 1.04 (0.97 to 1.12)	1 more per 1000 (from 1 fewer to 4 more)	VERY LOW	CRITICAL
Dementia - by progestogenic constituent, unknown recency, for 5 or more years use – Noresthisterone												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1179 cases 4906 controls	3.5%[4]	OR 1 (0.94 to 1.06)	0 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Dementia - by progestogenic constituent, unknown recency, for 3 or more years use – Dydrogesterone												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77 cases 366 controls	3.5%[4]	OR 0.88 (0.75 to 1.03)	4 fewer per 1000 (from 9 fewer to 1 more)	VERY LOW	CRITICAL
Dementia - by progestogenic constituent, unknown recency, for 5 or more years use – Medroxyprogesterone												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	538 cases 2223 controls	3.5%[4]	OR 1.01 (0.92 to 1.11)	0 more per 1000 (from 3 fewer to 4 more)	VERY LOW	CRITICAL
Dementia - by mode of administration (for combined with noresthisterone), unknown recency, for 5 to <10 years of use - Oral												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	147 cases 619 controls	3.5%[4]	OR 0.96 (0.79 to 1.17)	1 fewer per 1000 (from 7 fewer to 6 more)	VERY LOW	CRITICAL
Dementia - by mode of administration (for combined with noresthisterone), unknown recency, for 5 or more years of use - Transdermal												
Vinogradova	Nested case control	serious[1]	no serious	no serious	no serious	none	833 cases 3269		OR 1.04	1 more	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	no HRT	Relative (95% CI)	Absolute		
2021	study		inconsistency	indirectness	imprecision		controls	3.5%[4]	(0.96 to 1.13)	per 1000 (from 1 fewer to 4 more)		
Dementia, by age at first use, for 5-9 years use - <60 years												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1614 cases 6993 controls	3.5%[4]	OR 1.01 (0.95 to 1.07)	0 more per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Dementia, by age at first use, for 5-9 years use - 60 or older												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	831 cases 3411 controls	3.5%[4]	OR 0.98 (0.91 to 1.06)	1 fewer per 1000 (from 3 fewer to 2 more)	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; OR: odds ratio; NR: not reported
1 Serious risk of bias in the evidence contributing to outcomes as per ROBINS-I or CASP checklist
2 95% CI crosses 1 MID
3 No information provided for combined users in the specific subgroup for Imtiaz 2017, the number of events for all subgroups of combined users was for all subgroups: 74/2384 (3.1%)
4 Control group risk taken from Imtiaz 2017
5 95% CI crosses 2 MIDs

Table 5: Comparison 2: Oestrogen plus progestogen, continuous combined, versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, continuous combined	No HRT	Relative (95% CI)	Absolute		
Dementia, past users, >8 years since last use, by duration of use, ≤1 year use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	173 cases 1571 controls	3.5%[3]	HR 1.22 (1.04 to 1.43)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >1 to 4 years use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, continuous combined	No HRT	Relative (95% CI)	Absolute		
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	130 cases 1235 controls	3.5%[3]	HR 1.2 (1 to 1.44)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >4 to 8 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104 cases 837 controls	3.5%[3]	HR 1.44 (1.17 to 1.77)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >8 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51 cases 276 controls	3.5%[3]	HR 1.99 (1.46 to 2.71)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy
1 Serious risk in bias in the evidence contributing to outcomes as per CASP checklist
2 95% CI crosses 1 MID
3 Control group risk taken from Imtiaz 2017

Table 6: Comparison 3: Oestrogen plus progestogen, sequential combined, versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, sequential combined	No HRT	Relative (95% CI)	Absolute		
Dementia, past users >8 years since last use, by duration of use, ≤1 year use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	283 cases 2573 controls	3.5%[3]	HR 1.21 (1.06 to 1.38)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >1 to 4 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	243 cases 2256 controls	3.5%[3]	HR 1.22 (1.06 to 1.4)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >4 to 8 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	136 cases 1217 controls	3.5%[3]	HR 1.25 (1.04 to 1.5)	Not calculable	VERY LOW	CRITICAL
Dementia, past users >8 years since last use, by duration of use, >8 years use												
Pourhadi 2023	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32 cases 238 controls	3.5%[3]	HR 1.59 (1.09 to 2.32)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy
1 Serious risk of bias in the evidence contributing to outcomes as per CASP checklist
2 95% CI crosses 1 MID
3 Control group risk taken from Imtiaz 2017

Table 7: Comparison 4: Oestrogen plus progestogen, continuous combined, versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen	Placebo	Relative (95% CI)	Absolute		
Dementia (dementia at 4 years follow-up)												
WHIMS	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/2229 (1.8%)	21/2303 (0.91%)	RR 1.97 (1.16 to 3.33)	9 more per 1000 (from 1 more to 21 more)	MODERATE	CRITICAL
Alzheimer's or dementia mortality (at 18 years follow-up)												
WHI	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	223/8506 (2.6%)	233/8102 (2.9%)	HR 0.93 (0.77 to 1.12)	Not calculable	MODERATE	CRITICAL

CI: confidence interval; HR: hazard ratio; RR: risk ratio; WHI: Women's Health Initiative; WHIMS: Women's Health Initiative Memory Study

1 95% CI crosses 1 MID

Table 8: Comparison 5: Oestrogen-only versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen only	No HRT	Relative (95% CI)	Absolute		
Dementia, unknown recency by duration of use: <1 year use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR[3]	147/4153 3.5%[4]	HR 0.85 (0.49 to 1.47)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: < 1 year use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1608 cases 6255 controls	3.5%[4]	OR 1.05 (0.99 to 1.11)	2 more per 1000 (from 0 fewer to 4 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: 1 to 3 years use												
2[5]	Cohort studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	49 cases 39 controls and NR[3] exposed	147/4153 unexposed	HR 1.06 (0.78 to 1.44)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: 1 to 3 years use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen only	No HRT	Relative (95% CI)	Absolute		
2[6]	Nested case control studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1138 cases 4717 controls	3.5%[4]	OR 0.99 (0.93 to 1.07)	0 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >3 to 5 years use												
Imtiaz 2017	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR[3]	147/4153 (3.5%)	HR 1.1 (0.59 to 2.05)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >3 to 5 years use												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	778 cases 3240 controls	3.5%[4]	OR 0.92 (0.85 to 1)	3 fewer per 1000 (from 5 fewer to 0 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >5 to 10 years use												
2[5]	Cohort studies	serious[1]	serious[7]	no serious indirectness	very serious[2]	none	62 cases 50 controls and NR[3] exposed 147/4153 unexposed		HR 1.08 (0.65 to 1.78)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >5 to 10 years use												
2[6]	Nested case control studies	serious[1]	very serious[8]	no serious indirectness	very serious[2]	none	1798 cases 7469 controls	3.5%[4]	OR 0.73 (0.38 to 1.43) [range 0.50 (0.31 to 0.81), 0.99 (0.94 to 1.04)	9 fewer per 1000 (from 21 fewer to 14 more)	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >10 years use												
2[5]	Cohort studies	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	39 cases 56 controls and NR[3] exposed 147/4153 unexposed		HR 0.82 (0.55 to 1.21)	Not calculable	VERY LOW	CRITICAL
Dementia, unknown recency by duration of use: >10 years use												
2[6]	Nested case control studies	serious[1]	very serious[8]	no serious indirectness	very serious[2]	none	951 cases 4239 controls	3.5%[4]	OR 0.67 (0.32 to 1.39) [range 0.44 (0.26 to 0.74), 0.93 (0.86 to 1.01)]	11 fewer per 1000 (from 24 fewer to 13 more)	VERY LOW	CRITICAL
Dementia, current users unknown duration of use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen only	No HRT	Relative (95% CI)	Absolute		
Seshadri 2004	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4 cases 16 controls	3.5%[4]	OR 0.89 (0.35 to 2.26)	4 fewer per 1000 (from 22 fewer to 41 more)	VERY LOW	CRITICAL
Dementia - by constituent, unknown recency, for 5 or more years use - Conjugated equine estrogen												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1320 cases 5529 controls	3.5%[4]	OR 0.97 (0.91 to 1.04)	1 fewer per 1000 (from 3 fewer to 1 more)	VERY LOW	CRITICAL
Dementia - by constituent, unknown recency, for 5 or more years use – Estradiol												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1337 cases 5590 controls	3.5%[4]	OR 0.98 (0.91 to 1.04)	1 fewer per 1000 (from 3 fewer to 1 more)	VERY LOW	CRITICAL
Dementia - by mode of administration, unknown recency, for 5 to 14 years of use – Oral												
2[6]	Nested case control studies	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	132 cases 638 controls	3.5%[4]	OR 0.85 (0.7 to 1.03)	5 fewer per 1000 (from 10 fewer to 1 more)	VERY LOW	CRITICAL
Dementia - by mode of administration, unknown recency, for 5+ years of use – Transdermal												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	282 cases 1275 controls	3.5%[4]	OR 0.91 (0.79 to 1.05)	3 fewer per 1000 (from 7 fewer to 2 more)	VERY LOW	CRITICAL
Dementia, by age at first use, for 5-9 years use: <60 years												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	955 cases 3937 controls	3.5%[4]	OR 1.02 (0.94 to 1.1)	1 more per 1000 (from 2 fewer to 3 more)	VERY LOW	CRITICAL
Dementia, by age at first use, for 5-9 years use: 60 or older												
Vinogradova 2021	Nested case control study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	818 cases 3345 controls	3.5%[4]	OR 0.97 (0.9 to 1.05)	1 fewer per 1000 (from 3 fewer to 2 more)	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; OR: odds ratio; NR: not reported

1 Serious risk of bias in the evidence contributing to outcomes as per ROBINS-I, or CASP checklist
2 95% CI crosses 2 MIDs
3 No information provided for oestrogen users in the specific subgroup for Imtiaz 2017, the number of events for all subgroups of oestrogen users was 68/2298 (3%)
4 Control group risk taken from Imtiaz 2017
5 Imtiaz 2017; Paganini-Hill 2020
6 Paganini-Hill 1996; Vinogradova 2021
7 Serious heterogeneity unexplained by subgroup analysis
8 Very serious heterogeneity unexplained by subgroup analysis
9 95% CI crosses 1 MID

Table 9: Comparison 6: Oestrogen-only versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Dementia (dementia at 5 years follow-up)												
WHIMS	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28/1464 (1.9%)	19/1483 (1.3%)	RR 1.49 (0.84 to 2.66)	6 more per 1000 (from 2 fewer to 21 more)	MODERATE	CRITICAL
Alzheimer's or dementia mortality (at 18 years follow-up)												
WHI	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	127/5310 (2.4%)	175/5429 (3.2%)	HR 0.74 (0.59 to 0.93)	Not calculable	MODERATE	CRITICAL

CI: confidence interval; HR: hazard ratio; RR: risk ratio; WHI: Women's Health Initiative; WHIMS: Women's Health Initiative Memory Study
1 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

No economic evidence was identified which was applicable to this review question. For economic searches see Supplement 2.

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Excluded effectiveness studies

Table 10: Excluded studies and reasons for their exclusion

Study	Reason
Anonymous. (2004) Hormone therapy with oestrogen or oestrogen plus progesterone does not reduce the risk of dementia or mild cognitive impairment in older postmenopausal women. Evidence-Based Healthcare and Public Health 8(6): 396-397	- Publication is abstract only
Armstrong, Nicole M, Espeland, Mark A, Chen, Jiu-Chiuan et al. (2020) Associations of Hearing Loss and Menopausal Hormone Therapy With Change in Global Cognition and Incident Cognitive Impairment Among Postmenopausal Women. The journals of gerontology. Series A, Biological sciences and medical sciences 75(3): 537-544	- Outcomes - reported outcomes do not match the review protocols
Baik, S.H.; Baye, F.; McDonald, C.J. (2022) Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 7 million menopausal women over age 65: a retrospective observational study. medRxiv	- Study design - not a systematic review, randomised controlled trial, or observational study Preprint paper not peer-reviewed
Baldereschi, M, Di Carlo, A, Lepore, V et al. (1998) Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. Neurology 50(4): 996-1002	- Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Berent-Spillson, Alison, Kelley, Angela S, Persad, Carol C et al. (2018) Postmenopausal hormone treatment alters neural pathways but does not improve verbal cognitive function. Menopause (New York, N.Y.) 25(12): 1424-1431	- Outcomes - reported outcomes do not match the review protocols
Blumel, J E, Arteaga, E, Vallejo, M S et al. (2022) Association of bilateral oophorectomy and menopause hormone therapy with mild cognitive impairment: the REDLINC X study. Climacteric : the journal of the International Menopause Society 25(2): 195-202	- Outcomes - reported outcomes do not match the review protocols
Boyle, Christina P, Raji, Cyrus A, Erickson, Kirk I et al. (2021) Estrogen, brain structure, and cognition in postmenopausal women. Human brain mapping 42(1): 24-35	- Comparison - not placebo or no HRT
Brenner, D E, Kukull, W A, Stergachis, A et al. (1994) Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: a population-based case-control study. American journal of epidemiology 140(3): 262-7	- Intervention – oestrogen-only & combined HRT not reported separately Most women used progestogens, however analysis is based on the oestrogen prescriptions - not enough information regarding progestogen use
Brinton, RD, Nilsen, J, Breitner, JCS et al. (2003) Effects of estrogen plus progestin on risk of dementia Shumaker SA, Legault C, Rapp SR et al Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized	- Study design - not a systematic review, randomised controlled trial, or observational study

Study	Reason
controlled trial JAMA 2003;289: 2651-2662. Jama:-journal-of-the-american-medical-association 290(13): 1706-1708	Reply to Shumaker 2003 which has been assessed for inclusion separately
Cardinali, Camila A E F; Martins, Yandara A; Torrao, Andrea S (2021) Use of Hormone Therapy in Postmenopausal Women with Alzheimer's Disease: A Systematic Review. Drugs & aging 38(9): 769-791	- Population Systematic review checked for relevant studies but most are not relevant due to HRT use for treatment of dementia, or HRT not reported as oestrogen-only & combined separately. Any relevant studies have been included separately
Carlson, M C, Zandi, P P, Plassman, B L et al. (2001) Hormone replacement therapy and reduced cognitive decline in older women: the Cache County Study. Neurology 57(12): 2210-6	- Intervention – oestrogen-only & combined HRT not reported separately
Chang, Heidi, Kamara, Daniella, Bresee, Catherine et al. (2020) Short-term impact of surgically induced menopause on cognitive function and wellbeing in women at high risk for ovarian cancer following risk-reducing bilateral salpingo-oophorectomy. Menopause (New York, N.Y.) 28(4): 354-359	- Outcomes - reported outcomes do not match the review protocols
Chen, Lin, Zheng, Wei, Chen, Gang et al. (2022) Menopausal hormone therapy does not improve some domains of memory: A systematic review and meta-analysis. Frontiers in endocrinology 13: 894883	- Outcomes - reported outcomes do not match the review protocols
Costa, M M, Reus, V I, Wolkowitz, O M et al. (1999) Estrogen replacement therapy and cognitive decline in memory-impaired post-menopausal women. Biological psychiatry 46(2): 182-8	- Outcomes - reported outcomes do not match the review protocols
Craig, Michael C; Maki, Pauline M; Murphy, Declan G M (2005) The Women's Health Initiative Memory Study: findings and implications for treatment. The Lancet. Neurology 4(3): 190-4	- Cohort already included Rapid review of WHIMS results which have been reported on in Shumaker 2004
de Moraes, S A, Szklo, M, Knopman, D et al. (2001) Prospective assessment of estrogen replacement therapy and cognitive functioning: atherosclerosis risk in communities study. American journal of epidemiology 154(8): 733-9	- Outcomes - reported outcomes do not match the review protocols
Espeland, Mark A, Rapp, Stephen R, Manson, JoAnn E et al. (2017) Long-term Effects on Cognitive Trajectories of Postmenopausal Hormone Therapy in Two Age Groups. The journals of gerontology. Series A, Biological sciences and medical sciences 72(6): 838-845	- Outcomes - reported outcomes do not match the review protocols
Espeland, Mark A, Rapp, Stephen R, Shumaker, Sally A et al. (2004) Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291(24): 2959-68	- Outcomes - reported outcomes do not match the review protocols
Espeland, Mark A, Tindle, Hilary A, Bushnell, Cheryl A et al. (2009) Brain volumes, cognitive impairment, and conjugated equine estrogens. The journals of gerontology. Series A, Biological sciences and medical sciences 64(12): 1243-50	- Outcomes - reported outcomes do not match the review protocols
Espeland MA, Shumaker SA, Leng I, et al. (2013) Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med. 173(15):1429-36.	- Outcomes – reported outcomes do not match the review protocols
Etgen, A.M. (2008) Estrogens and Alzheimer's disease: Is cholesterol a link?. Endocrinology 149(9): 4253-4255	- Study design - not a systematic review,

Study	Reason
	randomised controlled trial, or observational study
Fillenbaum, G G, Hanlon, J T, Landerman, L R et al. (2001) Impact of estrogen use on decline in cognitive function in a representative sample of older community-resident women. American journal of epidemiology 153(2): 137-44	- Outcomes - reported outcomes do not match the review protocols
Fox, Molly; Berzuini, Carlo; Knapp, Leslie A (2013) Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. Psychoneuroendocrinology 38(12): 2973-82	- Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Gartlehner, Gerald, Patel, Sheila V, Feltner, Cynthia et al. (2017) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 318(22): 2234-2249	- Outcomes - reported outcomes do not match the review protocols Systematic review, included studies mostly do not meet protocol outcomes. Studies that do meet outcomes have already been included in the review
Gartlehner, Gerald, Patel, Sheila V, Viswanathan, Meera et al. (2017) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: An Evidence Review for the U.S. Preventive Services Task Force.	- Duplicate
Gleason, Carey E, Dowling, N Maritza, Wharton, Whitney et al. (2015) Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS medicine 12(6): e1001833-e1001833	- Outcomes - reported outcomes do not match the review protocols
Goveas, Joseph S, Espeland, Mark A, Woods, Nancy F et al. (2011) Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: the Women's Health Initiative Memory Study. Journal of the American Geriatrics Society 59(1): 57-66	- Comparison - not placebo or no HRT
Grady, Deborah, Yaffe, Kristine, Kristof, Margaret et al. (2002) Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. The American journal of medicine 113(7): 543-8	- Outcomes - reported outcomes do not match the review protocols
Han, Minjung, Chang, Jooyoung, Choi, Seulggie et al. (2021) Association of tibolone and dementia risk: a cohort study using Korean claims data. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 37(6): 567-571	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Henderson, V W, Benke, K S, Green, R C et al. (2005) Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. Journal of neurology, neurosurgery, and psychiatry 76(1): 103-5	- Intervention - oestrogen only & combined HRT not reported separately
Henderson, Victor W and Rocca, Walter A (2012) Estrogens and Alzheimer disease risk: Is there a window of opportunity?. Neurology 79(18): 1840-1841	- Study design - not a systematic review, randomised controlled trial, or observational study
Herrera, Alexandra Ycaza, Hodis, Howard N, Mack, Wendy J et al. (2017) Estradiol Therapy After Menopause Mitigates Effects of Stress on Cortisol and Working Memory. The Journal of clinical endocrinology and metabolism 102(12): 4457-4466	- Outcomes - reported outcomes do not match the review protocols
Hogervorst, E, Williams, J, Budge, M et al. (2000) The nature of the	- Study design -

Study	Reason
effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 101(3): 485-512	observational study: data on HRT use not collected at time of prescription or before the outcome was known Relevant studies checked for inclusion but most do not meet criteria due to data on HRT use collected after outcome was known. Other relevant studies have already been included
Hogervorst, Eef and Bandelow, Stephan (2010) Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. Maturitas 66(1): 56-71	- Outcomes - reported outcomes do not match the review protocols Studies included looking at cognitive function tests rather than dementia
Hogervorst, Eva, Yaffe, Kristine, Richards, Marcus et al. (2009) Hormone replacement therapy to maintain cognitive function in women with dementia. The Cochrane database of systematic reviews: cd003799	- Outcomes - reported outcomes do not match the review protocols Women included already had dementia at the start. Studies included in this review were looking at cognitive decline in women with dementia following HRT use
Imtiaz, Bushra, Tolppanen, Anna Maija, Solomon, Alina et al. (2017) Estradiol and Cognition in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Cohort Study. Journal of Alzheimer's disease : JAD 56(2): 453-458	- Intervention – oestrogen-only & combined HRT not reported separately
ISRCTN55999335 (2003) Wisdom-Cog: the effect of HRT on dementia and cognitive function Investigating the effect of hormone replacement therapy (HRT) on cognitive function in women post-menopause. https://doi.org/10.1186/ISRCTN55999335	- Study design - not a systematic review, randomised controlled trial, or observational study Clinical trial entry only
Jayachandran, Muthuvel, Miller, Virginia M, Lahr, Brian D et al. (2021) Peripheral Markers of Neurovascular Unit Integrity and Amyloid-beta in the Brains of Menopausal Women. Journal of Alzheimer's disease : JAD 80(1): 397-405	- Outcomes - reported outcomes do not match the review protocols
Jett, Steven, Malviya, Niharika, Schelbaum, Eva et al. (2022) Endogenous and Exogenous Estrogen Exposures: How Women's Reproductive Health Can Drive Brain Aging and Inform Alzheimer's Prevention. Frontiers in aging neuroscience 14: 831807	- Study design - not a systematic review, randomised controlled trial, or observational study
Kang, Jae H; Weuve, Jennifer; Grodstein, Francine (2004) Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 63(1): 101-7	- Outcomes - reported outcomes do not match the review protocols
Kantarci, Kejal, Lowe, Val J, Lesnick, Timothy G et al. (2016) Early Postmenopausal Transdermal 17beta-Estradiol Therapy and Amyloid-beta Deposition. Journal of Alzheimer's disease : JAD 53(2): 547-56	- Outcomes - reported outcomes do not match the review protocols
Kantarci, Kejal, Tosakulwong, Nirubol, Lesnick, Timothy G et al. (2018) Brain structure and cognition 3 years after the end of an early menopausal hormone therapy trial. Neurology 90(16): e1404-e1412	- Outcomes - reported outcomes do not match the review protocols
Kawas, C, Resnick, S, Morrison, A et al. (1997) A prospective study of estrogen replacement therapy and the risk of developing	- Outcomes - relevant confounders not adjusted for

Study	Reason
Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 48(6): 1517-21	Study did not present the results of the analysis adjusted for confounders - only unadjusted ratios are presented
Kerwin, Diana R, Gaussoin, Sarah A, Chlebowski, Rowan T et al. (2011) Interaction between body mass index and central adiposity and risk of incident cognitive impairment and dementia: results from the Women's Health Initiative Memory Study. Journal of the American Geriatrics Society 59(1): 107-12	- Outcomes - reported outcomes do not match the review protocols
Kim, Hyewon, Yoo, Juhwan, Han, Kyungdo et al. (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	- Intervention – oestrogen-only & combined HRT not reported separately
Kim, Yu Jin, Soto, Maira, Branigan, Gregory L et al. (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	- Intervention – oestrogen-only & combined HRT not reported separately Oestrogen-only and combined HRT reported individually without information on recency or duration of use - this was only reported for any HRT
Kotsopoulos, Joanne, Kim, Shana J, Armel, Susan et al. (2021) An evaluation of memory and attention in BRCA mutation carriers using an online cognitive assessment tool. Cancer 127(17): 3183-3193	- Intervention – oestrogen-only & combined HRT not reported separately
Lan, Yu-Long, Zou, Shuang, Zhang, Changfu et al. (2016) Update on the effect of estradiol in postmenopause women with Alzheimer's disease: a systematic review. Acta neurologica Belgica 116(3): 249-57	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen Systematic review focusing on the levels of oestrogen in postmenopausal women, or the use of oestrogen for the treatment of Alzheimer's disease
LeBlanc, E S, Janowsky, J, Chan, B K et al. (2001) Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 285(11): 1489-99	- Outcomes - reported outcomes do not match the review protocols
Leblanc, E.S., Janowsky, J., Chan, B.K.S. et al. (2001) Hormone replacement therapy and cognition: Systematic review and meta-analysis. JAMA 285(11): 1489-1499	- Duplicate
Leblanc, Erin; Chan, Benjamin; Nelson, Heidi D (2002) Hormone Replacement Therapy and Cognition.	- Duplicate
Maki, Pauline M (2005) A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. Annals of the New York Academy of Sciences 1052: 182-97	- Outcomes - reported outcomes do not match the review protocol Systematic review, studies checked for relevance but not included as they report on cognitive function and not dementia or mortality from dementia
Maki, Pauline M; Girard, Lucille M; Manson, JoAnn E (2019) Menopausal hormone therapy and cognition. BMJ (Clinical research ed.) 364: l877	- Study design - not a systematic review, randomised controlled trial,

Study	Reason
	or observational study
Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen et al. (2017) Long-term hormone therapy for perimenopausal and postmenopausal women. The Cochrane database of systematic reviews 1: cd004143	- Cohort already included Relevant studies in this systematic review have already been included (WHIMS cohort)
Mikkola, Tomi S, Savolainen-Peltonen, Hanna, Tuomikoski, Pauliina et al. (2017) Lower Death Risk for Vascular Dementia Than for Alzheimer's Disease With Postmenopausal Hormone Therapy Users. The Journal of clinical endocrinology and metabolism 102(3): 870-877	- Comparison - not placebo or no HRT Comparator is age-standard female population, which included HRT users. No appropriate adjustments for any other confounders made
O'Brien, Jacqueline, Jackson, John W, Grodstein, Francine et al. (2014) Postmenopausal hormone therapy is not associated with risk of all-cause dementia and Alzheimer's disease. Epidemiologic reviews 36: 83-103	- Intervention – oestrogen-only & combined HRT not reported separately Systematic review checked for relevant studies. Most are already included in the review, but some are not relevant as HRT not reported as oestrogen-only & combined separately
Paganini-Hill, A and Henderson, V W (1994) Estrogen deficiency and risk of Alzheimer's disease in women. American journal of epidemiology 140(3): 256-61	- Cohort already included Same cohort included in a later publication with a longer follow-up period (Paganini-Hill 1996)
Petitti, Diana B, Buckwalter, J Galen, Crooks, Valerie C et al. (2002) Prevalence of dementia in users of hormone replacement therapy as defined by prescription data. The journals of gerontology. Series A, Biological sciences and medical sciences 57(8): m532-8	- Intervention – oestrogen-only & combined HRT not reported separately
Petitti, Diana B, Crooks, Valerie C, Chiu, Vicki et al. (2008) Incidence of dementia in long-term hormone users. American journal of epidemiology 167(6): 692-700	- Intervention – oestrogen-only & combined HRT not reported separately Oestrogen-only and combined HRT reported individually without information on recency or duration of use - this was only reported for any HRT
Prince, M (2000) A randomised placebo-controlled trial of the effect of hormone replacement therapy on dementia and cognitive function in post-menopausal women (WISDOM-COG). Current controlled trials [www.controlled-trials.com]	- Study design - not a systematic review, randomised controlled trial, or observational study Clinical trial protocol only
Rapp, Stephen R, Espeland, Mark A, Manson, Joann E et al. (2013) Educational attainment, MRI changes, and cognitive function in older postmenopausal women from the Women's Health Initiative Memory Study. International journal of psychiatry in medicine 46(2): 121-43	- Outcomes - reported outcomes do not match the review protocols
Rasgon, Natalie L, Geist, Cheri L, Kenna, Heather A et al. (2014) Prospective randomized trial to assess effects of continuing hormone therapy on cerebral function in postmenopausal women at risk for dementia. PloS one 9(3): e89095	- Outcomes - reported outcomes do not match the review protocols
Reszegi, Katalin (2022) Verbal cognition and hormone replacement	- Study design - not a

Study	Reason
during menopause: A meta-analysis. Dissertation Abstracts International: Section B: The Sciences and Engineering 83(3b): no-specified	systematic review, randomised controlled trial, or observational study Dissertation
Rice, M M, Graves, A B, McCurry, S M et al. (2000) Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: The Kame Project. Archives of internal medicine 160(11): 1641-9	- Outcomes - relevant confounders not adjusted for
Roberts, Rosebud O, Cha, Ruth H, Knopman, David S et al. (2006) Postmenopausal estrogen therapy and Alzheimer disease: overall negative findings. Alzheimer disease and associated disorders 20(3): 141-6	- Comparison - not placebo or no HRT Included women who used HRT for <6 months in comparator
Rocca, Walter A, Lohse, Christine M, Smith, Carin Y et al. (2021) Association of Premenopausal Bilateral Oophorectomy With Cognitive Performance and Risk of Mild Cognitive Impairment. JAMA network open 4(11): e2131448	- Outcomes - reported outcomes do not match the review protocols
Ross, Colin (2022) Estrogen treatments and risk of Alzheimer's disease: A systematic review. Dissertation Abstracts International: Section B: The Sciences and Engineering 83(2b): no-specified	- Study design - not a systematic review, randomised controlled trial, or observational study
Ryan, J, Carriere, I, Scali, J et al. (2009) Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C Study. Neurology 73(21): 1729-37	- Intervention – oestrogen-only & combined HRT not reported separately
Sano, Mary, Jacobs, Diane, Andrews, Howard et al. (2008) A multi-center, randomized, double blind placebo-controlled trial of estrogens to prevent Alzheimer's disease and loss of memory in women: design and baseline characteristics. Clinical trials (London, England) 5(5): 523-33	- Outcomes - reported outcomes do not match the review protocols
Savolainen-Peltonen, Hanna, Rahkola-Soisalo, Paivi, Hoti, Fabian et al. (2019) Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ (Clinical research ed.) 364: l665	- Outcomes - relevant confounders not adjusted for
Schneider, Lon S (2004) Estrogen and dementia: insights from the Women's Health Initiative Memory Study. JAMA 291(24): 3005-7	- Study design - not a systematic review, randomised controlled trial, or observational study
Shao, Huibo, Breitner, John C S, Whitmer, Rachel A et al. (2012) Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology 79(18): 1846-52	- Intervention – oestrogen-only & combined HRT not reported separately Data by type of HRT not reported by recency or duration
Shumaker, S.A., Reboussin, B.A., Espeland, M.A. et al. (1998) The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Controlled Clinical Trials 19(6): 604-621	- Study design - not a systematic review, randomised controlled trial, or observational study Protocol only
Song, Yu-Jia, Li, Shu-Ran, Li, Xiao-Wan et al. (2020) The Effect of Estrogen Replacement Therapy on Alzheimer's Disease and Parkinson's Disease in Postmenopausal Women: A Meta-Analysis. Frontiers in neuroscience 14: 157	- Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known Systematic review. Studies checked for inclusion but do

Study	Reason
	not meet protocol criteria due to study design
Stute, Petra, Wienges, Johanna, Koller, Anne-Sophie et al. (2021) Cognitive health after menopause: Does menopausal hormone therapy affect it?. Best practice & research. Clinical endocrinology & metabolism 35(6): 101565	- Population Systematic review checked for relevant studies but most are not relevant due to HRT use for treatment of dementia, or HRT not reported as oestrogen-only & combined separately. Any relevant studies have been included separately
Tang, M X, Jacobs, D, Stern, Y et al. (1996) Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet (London, England) 348(9025): 429-32	- Outcomes - relevant confounders not adjusted for
Vickers, Madge R, Martin, Jeannett, Meade, Tom W et al. (2007) The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC women's health 7: 2	- Study design - not a systematic review, randomised controlled trial, or observational study Study protocol only
Viscoli, Catherine M, Brass, Lawrence M, Kernan, Walter N et al. (2005) Estrogen therapy and risk of cognitive decline: results from the Women's Estrogen for Stroke Trial (WEST). American journal of obstetrics and gynecology 192(2): 387-93	- Outcomes - reported outcomes do not match the review protocols
Waring, S C, Rocca, W A, Petersen, R C et al. (1999) Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. Neurology 52(5): 965-70	- Outcomes - relevant confounders not adjusted for
Wharton, Whitney, Baker, Laura D, Gleason, Carey E et al. (2011) Short-term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. Journal of Alzheimer's disease : JAD 26(3): 495-505	- Outcomes - reported outcomes do not match the review protocol Women who have Alzheimer's Disease included at the start of the study, therefore incidence of dementia not reported
Whitmer, Rachel A, Quesenberry, Charles P, Zhou, Jufen et al. (2011) Timing of hormone therapy and dementia: the critical window theory revisited. Annals of neurology 69(1): 163-9	- Intervention – oestrogen-only & combined HRT not reported separately
Wu, Minghua, Li, Min, Yuan, Jun et al. (2020) Postmenopausal hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease: A systematic review and time-response meta-analysis. Pharmacological research 155: 104693	- Outcomes - reported outcomes do not match the review protocol Systematic review. Included studies checked for relevance, most have been included, however others have not been included in the review because they do not report the outcomes in the protocol
Yaffe, K, Barrett-Connor, E, Lin, F et al. (2002) Serum lipoprotein levels, statin use, and cognitive function in older women. Archives of neurology 59(3): 378-384	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Yesufu, Amina; Bandelow, Stephan; Hogervorst, Eva (2007) Meta-analyses of the effect of hormone treatment on cognitive function in postmenopausal women. Women's health (London, England) 3(2): 173-94	- Study design - not a systematic review, randomised controlled trial, or observational study

Study	Reason
Yoo, J E, Shin, D W, Han, K et al. (2020) Female reproductive factors and the risk of dementia: a nationwide cohort study. European journal of neurology 27(8): 1448-1458	- Intervention – oestrogen-only & combined HRT not reported separately
Yoon, Byung-Koo, Chin, Juhee, Kim, Jong-Won et al. (2018) Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. Menopause (New York, N.Y.) 25(8): 870-876	- Outcomes - reported outcomes do not match the review protocol
Zec, R.F. and Trivedi, M.A. (2002) Early termination of WHI estrogen-progestin trial: Effect on cognitive aging and dementia risk studies [3]. Climacteric 5(3): 304	- Study design - not a systematic review, randomised controlled trial, or observational study Comment review on ongoing trial but no results reported in this publication
Zec, Ronald F and Trivedi, Mehul A (2001) Hormonal replacement therapy and cognition in postmenopausal women. JAMA: Journal of the American Medical Association 285(23): 2974-2975	- Study design - not a systematic review, randomised controlled trial, or observational study
Zhou, Huan-Huan, Yu, Zengli, Luo, Lan et al. (2021) The effect of hormone replacement therapy on cognitive function in healthy postmenopausal women: a meta-analysis of 23 randomized controlled trials. Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society 21(6): 926-938	- Outcomes - reported outcomes do not match the review protocol

Excluded economic studies

No economic evidence was identified for this review. See Supplement 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

The research recommendation from the 2015 guideline for this topic was retained but reworded from 'What are the effects of early HRT use on the risk of dementia?' to 'What are the effects of HRT use on the risk of dementia?' The committee decided to remove 'early' because it is difficult to define what 'early' means in the context of taking HRT for menopause symptoms and also because there is still relatively little research addressing this topic so keeping the question broad would encourage more research than restricting it to 'early HRT' only.

Additionally, there are overarching research recommendations related to all health outcomes addressed in this guideline update (including dementia), for:

- trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

Appendix L Absolute risk tables and calculations

Absolute risk tables and calculations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing dementia?

Absolute risks were calculated from the data available in the Women's Health Initiative Memory Study (WHIMS). They are specific to women who start HRT at the age of 65+ years, and use for either 4 or 5 years duration, depending on the duration of use in the trial.

The number of dementia cases in people who are not HRT users, per 1000, has been calculated using the data from the WHIMS. The number of cases for people who are not HRT users differs between the tables for combined HRT and oestrogen-only. Although in both tables they are not HRT users, the numbers differ due to 2 different cohorts in the placebo arms of the study.

Table 11: Summary of dementia cases with current use of combined HRT in people who, if they used it, started HRT at 65 or over and used it for 4 years

	65+ years old
Number of dementia cases over a 4-year period per 1000 people who are not HRT users	9
Number of dementia cases over a 4-year period per 1000 people who are HRT users	18

In Table 11 the follow-up period from the start of HRT use to the time of diagnosis was approximately 4 years.

Table 12: Summary of dementia cases with current use of oestrogen-only HRT in people who, if they used it, started HRT at 65 or over and used it for 5 years

	65+ years old
Number of dementia cases over a 5-year period per 1000 people who are not HRT users	13
Number of dementia cases over a 5-year period per 1000 people who are HRT users	19 NS

In Table 1112, NS means that the difference between a figure for HRT users and the corresponding figure for non-HRT users is non-significant.

In Table 12, the follow-up period from the start if HRT use to the time of diagnosis was approximately 5 years.