National Institute for Health and Care Excellence

Draft for consultation

Menopause (update)

[I] Early menopause

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.3.3, 1.4.2, 1.5.11 and 1.6.4 as well as the associated absolute number tables and research recommendation 1 in the NICE guideline

November 2023

Draft for consultation

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Early menopause

Review question

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 and loss of muscle mass and strength?

Introduction

Menopause occurring between the age of 40 to 45 years is defined as early menopause and is experienced by around 8% of women. In the short-term early menopause may cause symptoms and psychological distress. Whether early menopause affects long-term health is uncertain, but it has been proposed as a risk factor for adverse outcomes such as cardiovascular disease and osteoporosis. Early menopause may also reduce the risk of breast cancer. The relative risks and benefits of HRT after early menopause are poorly understood and this review aims to quantify the impact of HRT on long-term health in people with early menopause.

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 early menopause aged 40 to 44

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

Comparison	• Placebo treatment • No HRT

Outcome	**Critical**
	• Death from any cause[1]
	• Venous thromboembolism
	• Cardiovascular disease
	• Type 2 diabetes:
	  ○ HbA1c
	• Osteoporosis:
	  ○ vertebral fracture
	  ○ hip fracture
	• Loss of muscle mass and strength and function:
	  ○ sarcopenia
	  ○ falls
	• Incidence of breast cancer
	• Incidence of endometrial cancer

	• Incidence of ovarian cancer
	• Dementia
	  ○ cognitive decline measured using validated tools (not self-reported) (such as verbal word list recall; verbal fluency test, speed test, executive function tests)
	Important
	• Type 2 diabetes:
	  ○ medication use (self-reported)
	• Osteoporosis:
	  ○ fractures other than vertebral or hip
	  ○ bone mineral density

HRT: hormone replacement therapy.
1. Death from any cause will be limited to RCT data only

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

One study was included for this review, an individual participant data (IPD) meta-analysis of 24 observational studies and 6 RCTs (CGHFB 2019). This study reported a subgroup analysis of women aged 40 to 44 relevant to this evidence review.

The included study is 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	Interventions	Comparison	Outcomes	Comments
Collaborative Group on Hormonal Factors in Breast 2019 Nested case control (meta-	Number of studies=24 prospective cohort studies N=490994 women	• Oestrogen-only HRT • Oestrogen plus progestogen HRT	• No HRT use (prospective studies) • Placebo (RCTs)	• Incidence of breast cancer Subgroups: • Current/past HRT use • Age at first use	Confounders adjusted for: • family history (first degree relative with breast cancer • alcohol

Study	Population	Interventions	Comparison	Outcomes	Comments
analysis of prospective cohort studies using individual participant data Meta-analysis of RCTs	Sample size was not reported separately for the 40-44 age group) but overall: Age, mean (SD): 65 (7) years Number of studies= 6 RCTs N=13165 women (oestrogen-only studies) N=24919 women (oestrogen plus progestogen studies) Age, mean (SD): 63.5 (NR) years				consumption • reproductive history • age at menopause

HRT: hormone replacement therapy; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in Appendix D. No meta-analysis was conducted (and so there are no 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.

There was no evidence identified for the outcomes: death from any cause, venous thromboembolism, cardiovascular disease, type 2 diabetes, osteoporosis, loss of muscle mass and strength and function, incidence of endometrial cancer, incidence of ovarian cancer or dementia.

There was also no evidence identified for the subgroups: time since menopause at first use, constituent, mode of administration, progestogenic constituent, length of cycle, surgical menopause, BMI, or factors identified in the equalities section of the scope.

Oestrogen-progestogen combined HRT versus no HRT

Low to high quality evidence from one study indicated that current oestrogen-progestogen combined HRT users who initiated HRT at ages 40 to 44 years had an increased breast cancer risk when duration of use was over 1 years of use, and the risk increased with longer durations of use.

Moderate quality evidence from one study indicated that past oestrogen-progestogen combined HRT users who initiated HRT at ages 40 to 44 years had an increased breast cancer risk when duration of use was between 1 to 4 years, and 10 years or more.

Oestrogen-only HRT versus no HRT

Low to high quality evidence from one study indicated that current oestrogen-only HRT users who initiated HRT at ages 40 to 44 years had an increased breast cancer risk when duration of use was 5 years or more, and the risk increased with longer durations of use.

Moderate quality evidence from one study indicated that past oestrogen-only HRT users who initiated HRT at ages 40 to 44 years had an increased breast cancer risk when duration of use was 10 years or more.

See Appendix F for full GRADE tables and Appendix L for absolute risk 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 K.

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

Critical outcomes were venous thromboembolism, cardiovascular disease, dementia, type 2 diabetes, osteoporosis (vertebral or hip fractures), loss of muscle mass and strength and function (sarcopenia or falls), incidence of breast cancer, incidence of endometrial cancer, incidence of ovarian cancer because they are health conditions that can severely impact quality of life by causing disability or reducing length of life. Death from any cause was also a critical outcome. This was chosen because HRT could have a variety of different positive and negative effects on health, but any serious overall positive or negative effect should be apparent as a difference in overall mortality.

Fractures other than vertebral or hip were selected as an important outcome because they indicate osteoporosis but generally have less of an impact on quality of life than vertebral or hip fractures. Self-reported medication use, and bone mineral density were chosen as

important outcomes because they are surrogates for type 2 diabetes and osteoporosis respectively.

The quality of the evidence

The quality of evidence was assessed using GRADE and ranged from low to high. Evidence quality was downgraded because of imprecision in the relative effect estimate. There was a lack of evidence for all outcomes except for incidence of breast cancer. For this reason, the committee based the recommendations largely on their experience and expertise.

Benefits and harms

Whilst the included systematic review included evidence from both RCTS and observational studies, since the population of the RCT evidence did not meet the inclusion criteria based on age (40-44 years), therefore recommendations were based on observational evidence only.

Identifying perimenopause and menopause

The committee discussed that there was a lack of research around early menopause in different ethnic groups. However, the committee was aware from knowledge and experience that people from different ethnic backgrounds may be more likely to experience early menopause than people from white backgrounds. The committee agreed that service providers should be aware of this in order to correctly diagnose symptoms of the menopause in this population.

Discussing treatment options - HRT

It was acknowledged that the review question was limited to the risks and benefits associated with HRT in early menopause compared to people experiencing early menopause not taking HRT. The management of early menopause was not part of this update. The committee agreed that, to a certain extent, the role of HRT for early menopause mirrors the role of HRT for premature ovarian insufficiency. The committee considered the possibility that, like premature ovarian insufficiency, early menopause may either increase or decrease the baseline risk of some health outcomes. Although there is little evidence of the impact of HRT on health outcomes in people with premature ovarian insufficiency, it is current practice for this group to take HRT routinely.

Some of committee noted that the situation is similar for early menopause, with routine HRT being current practice. Hormone therapy might reverse some of the alterations to baseline risk of health outcomes in people with early menopause, but the committee did not review evidence on this. This was specifically discussed in the context of breast cancer baseline risk, where some committee members noted that taking HRT would return the lowered risk back to baseline. Given that early menopause as a risk factor for health outcomes was not the topic that was reviewed, the committee did not have the evidence to recommend HRT to address such risks and stipulate the duration of its usage. The committee therefore did not comment on this but stated that the risks and benefits of HRT for health outcomes may lie somewhere between the younger (POI) group and people who receive HRT for menopause symptoms at the average age of menopause (45 and older). Given these considerations the committee decided to emphasise that when discussing HRT the person’s age should be one of the important factors that should be considered. Baseline risks of specific health outcomes and the benefits and risks of hormone replacement therapy (HRT) all change with a person’s age at the start of the menopause transition, as well as with their individual circumstances and risk factors. As a result, the best parameters of HRT prescription are different from one person to another and should be carefully chosen with, and for, each person.

Review and referral for any treatment for menopause symptoms

Based on experience the committee noted that some people can be distressed by the diagnosis of menopause and the associated symptoms that they experience at an earlier age than expected and earlier than their peers. The committee noted that people may not want to share their experiences related to early menopause with their peers because of it being outside the norm leading to feelings of isolation. They also noted that people have children later in life and that it could be the case that they were planning pregnancy and not being able to conceive may cause distress. They noted that people may need support and if a person is experiencing emotional distress to a level that raises concerns they agreed that referral to specialist psychological services may be necessary. They agreed that not providing support and if needed onward referral would be unethical and that this is usual practice when a level of emotional distress reaches a threshold of clinical concern.

Effects of HRT on health outcomes in early menopause

Apart from evidence related to breast cancer, no other evidence on the impact of HRT on any health outcomes was identified. For people with premature ovarian insufficiency, HRT is offered for bone health and fracture prevention (because oestrogen helps maintain bone density) as well as cardiovascular health (because oestrogen and progestogens play important roles in maintaining the health and function of blood vessels). No evidence was identified relating to the impact of HRT on these outcomes in people experiencing early menopause.

The committee discussed that the evidence showed an increased risk of breast cancer for people with early menopause who used HRT, when compared to those not using HRT. They discussed that the role of HRT for early menopause mirrors that of premature ovarian insufficiency to a certain extent. Although there is little evidence of the impact of HRT on health outcomes in people with premature ovarian insufficiency it is current practice for this group to take HRT routinely. The committee acknowledged that the situation is similar for early menopause, with routine HRT being current practice. The committee discussed that the age cut-offs defining premature ovarian insufficiency, early menopause and typical menopause were somewhat arbitrary. They discussed that the risks and benefits of either taking or not taking HRT for people with early menopause are likely to lie somewhere between those for people with premature ovarian insufficiency and those for people aged 45 or over (where there is more evidence about these risks and benefits) – see also the ‘other factors the committee took into account’ section.

There was evidence of an increased risk of breast cancer for people with early menopause who used HRT compared to those not using HRT. The committee decided that it was important to explain this to the person so that they can make an informed decision.

Research recommendation

Due to the lack of evidence for most of the outcomes of interest in early menopause and the lack of evidence related to ethnicity, the committee agreed to make a research recommendation (see Appendix K) and identified people of different ethnic background as an important subgroup.

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 in people with early menopause on all-cause mortality and developing: venous thromboembolism, cardiovascular disease, type 2 diabetes, breast cancer, endometrial cancer, ovarian cancer, osteoporosis, dementia and loss of muscle mass and strength. Whilst recommendations in this area will lead to people being better informed about treatment decisions, it is unclear how such information will change treatment decisions and how these will impact upon overall

resource use. It would however be unethical to prevent such information being discussed with patients even if it did lead to an increase in resource use through changes in treatment decisions.

Recommendations making people aware that people with ethnic minority backgrounds may experience menopause earlier may increase diagnosis. This will lead to higher treatment costs in the short term. Earlier identification is likely to lead to improved outcomes from treatment and a reduction in healthcare contacts, reducing costs, to investigate other incorrect diagnoses and through better management of any bothersome symptoms associated with the menopause.

The committee noted that giving people in early menopause access to support or onward referral to psychological services if needed may increase referrals and resource use. However, the committee noted that it would be unethical not to provide support to someone when there is clinical concern about their psychological health. They also agreed that this was largely current practice and therefore the increase in referrals would be relatively small.

Other factors the committee took into account

The committee was aware that HRT after surgical menopause for people with high familial risk of ovarian cancer is within the scope of the NICE guideline on ovarian cancer: identifying and managing familial and genetic risk. This guideline is in development and is expected to be published in March 2024.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.3, 1.4.2, 1.5.11 and 1.6.4 as well as the associated absolute number tables and research recommendation 1 (on the impact of HRT on health outcomes in early menopause) in the NICE guideline.

References – included studies

Effectiveness

CGHFB 2019

Collaborative Group on Hormonal Factors in Breast, Cancer (2019) Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet (London, England) 394(10204): 1159-1168

Appendices

Appendix A Review protocols

Review protocol for review question: 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 and loss of muscle mass and strength?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362368
1.	Review title	Effects of hormone replacement therapy taken by women, non-binary and trans people with early menopause
2.	Review question	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
3.	Objective	To update the recommendations in NG23

ID	Field	Content
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: • Date • English language only • Human studies only • RCTs, Systematic Reviews and Observational studies Conference abstracts will be excluded from the search results 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 early menopause aged 40 to 44
7.	Intervention	HRT* • Oestrogen-only

ID	Field	Content

		• 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. 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 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 (for example: BMI, family history, lifestyle factors (smoking or alcohol intake), reproductive factors, education, socioeconomic status)
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• Death from any cause* • Venous thromboembolism • Cardiovascular disease

ID	Field	Content

		• Type 2 diabetes:
		  ○ HbA1c
		• Osteoporosis:
		  ○ vertebral fracture
		  ○ hip fracture
		• Loss of muscle mass and strength and function:
		  ○ sarcopenia
		  ○ falls
		• Incidence of breast cancer
		• Incidence of endometrial cancer
		• Incidence of ovarian cancer
		• Dementia
		  ○ cognitive decline measured using validated tools (not self-reported) (such as verbal word list recall; verbal fluency test, speed test, executive function tests)
		
		*Death from any cause will be limited to RCT data only

13.	Secondary outcomes (important outcomes)	• Type 2 diabetes:
		  ○ medication use (self-reported)
		• Osteoporosis:
		  ○ fractures other than vertebral or hip
		  ○ bone mineral density

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

ID	Field	Content
		criteria once the 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 • Tierney 2015 checklist for individual participant data meta-analyses of randomised controlled trials (Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. (2015) Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLoS Med 12(7): e1001855) 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:**

ID	Field	Content
		• Mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • 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:
		• 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) [Note it is essential to use the template text here to enable PROSPERO to recognise this as a NICE protocol]		
25.	Review team members	NGA Senior Systematic Reviewer . National Institute for Health and Care Excellence NGA Systematic Reviewer . National Institute for Health and Care Excellence		
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	crd.york.ac.uk/PROSPERO/display_record.php?RecordID=362368	
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	Breast Neoplasms; Cardiovascular Diseases; Dementia; Diabetes Mellitus, Type 2; Endometrial Neoplasms; Oestrogen Replacement Therapy; Female; Humans; Menopause; Muscles; Osteoporosis; Ovarian Neoplasms; Venous Thromboembolism	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		X	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; CRD: Centre for Reviews and Dissemination; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; HRT: hormone replacement therapy; INAHTA: International Network of Agencies for 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 question: 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 and loss of muscle mass and strength?

There was a combined literature search strategies for 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
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Estrogens/	97369

#	Searches	
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
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201

#	Searches	
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
99	or/93-98	6058843
100	92 not 99	34708

#	Searches	
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

Database: Embase <1974 to 2022 September 30>

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
9	exp *estrogen/	126164
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068

#	Searches	
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
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963

#	Searches	
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
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242

#	Searches	
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

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

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
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	4482

#	Searches	
	oestriol*).ti.	
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 or femur* or hip* or lumbar)).ti,ab,mh.	1936
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357

#	Searches	
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
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0

#	Searches	
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
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

#	Searches	
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56

Database: Cochrane Central Register of Controlled Trials (CENTRAL) 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
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

Database: Epistemonikos

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

#	Searches	
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

#	Searches	
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
55	26 and 54	849

Database: Embase <1974 to 2022 July 27>

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

#	Searches	
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
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

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

3 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

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

#	Searches	
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
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

#	Searches	
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

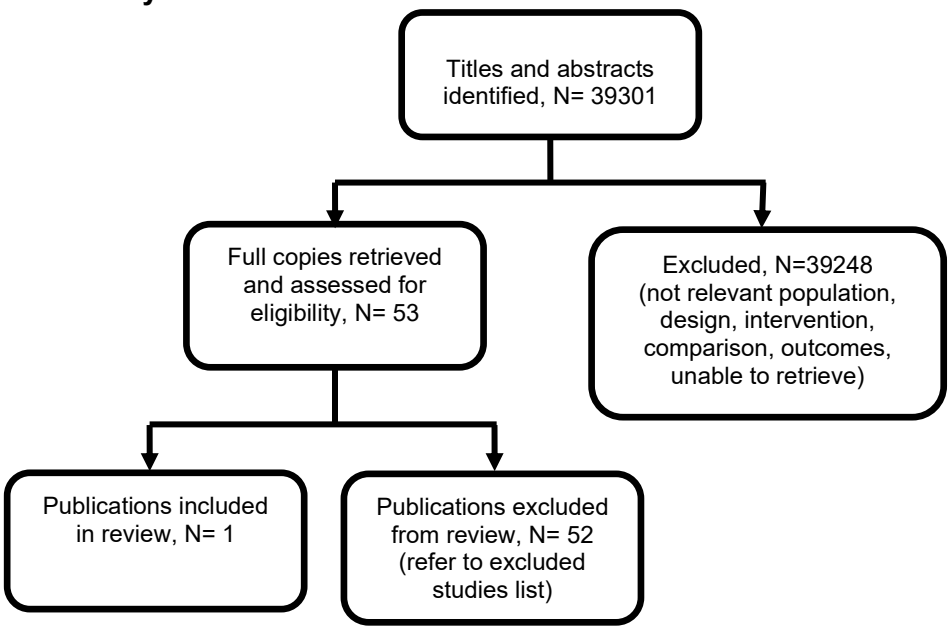
Date of last search: 28/07/2022

#	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 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 and loss of muscle mass and strength?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: 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 and loss of muscle mass and strength?

Table 4: Evidence tables

Collaborative Group on Hormonal Factors in Breast, 2019

Bibliographic Reference Collaborative Group on Hormonal Factors in Breast, Cancer; Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence.; Lancet (London, England); 2019; vol. 394 (no. 10204); 1159-1168

Study details

Country/ies where study was carried out	Countries across Europe and North America
Study type	Nested case-control (meta-analysis of prospective cohort studies using individual participant data) Meta-analysis of randomised controlled trials (RCT)
Inclusion criteria	Prospective studies: • Nested case-control design, with up to 4 randomly selected controls per case of invasive breast cancer. • Post menopausal women defined as known age at natural menopause (or bilateral oopherectomy) or unknown age at menopause but at least 55 years. • Included at least 1000 cases after year 2001. • Individual information on the type and timing of MHT use. • Individual information on body-mass index. RCTs:

	• Included at least 1000 cases after year 2001. • Individual information on the type and timing of MHT use. • Individual information on body-mass index.
Exclusion criteria	• Younger than 55 with a hysterectomy but unknown age at menopause
Patient characteristics	Prospective studies (average across 24 studies): • Age at diagnosis, years - mean (SD): • 65 (7) • Median (IQR) year of diagnosis of cases: 2005 (2000, 2009) RCTs: • Age at entry, years – mean: • 63.5
Intervention/control	Intervention: • Use of oestrogen-only hormone replacement therapy • Use of oestrogen plus progestogen hormone replacement therapy Control: • Non-users of HRT (prospective studies) • Placebo (RCTs)
Duration of follow-up	RCTs: Oestrogen-only: Approximate years in trial and later follow-up: 6.7 + 6 Oestrogen plus progesterone: Approximate years in trial and later follow-up: 5.6 + 7
Source of funding(s)	Cancer Research UK and the Medical Research Council

Sample size	Prospective studies (numbers not reported separately for the 40-44 age group): • N=490994 • Cases: n=108647 • Controls: n=382347 RCTs: Oestrogen-only: • N=13165 • Intervention: n=6530 • Control: n=6635 Oestrogen plus progestogen: • N=24919 • Intervention: n=12664 • Control: n=12255
Other information	Retrospective studies were included in the meta-analysis but excluded from this review as there was uncertainty over the recording of HRT use, and was not all collected by pharmacy data. Randomised controlled trials did not meet all of the eligibility criteria. They were not included in the main analysis but separately included. The combined effect estimates have been used in this review but analysed separately. Adjusted for: • Family history (first degree relative with breast cancer) • alcohol consumption • reproductive history (nulliparous, and, among parous women, by parity and age at first birth) • age at menopause.

Prospective studies:

Oestrogen-progestogen combined - current users (aged 40 to 44 at first use of HRT)*

Outcome – incidence of breast cancer	HRT users vs HRT never-users
Current use, Duration <1 year use Relative risk/95% CI	0.68 (0.09 – 5.33)
Current use, duration 1-4 years Relative risk/95% CI	1.74 (1.16 – 2.61)
Current use, duration 5-9 years Relative risk/95% CI	2.18 (1.74 – 2.74)
Current use, duration 10-14 years Relative risk/95% CI	2.26 (1.95 – 2.63)
Current use, duration of use 15 or more years Relative risk/95% CI	2.58 (2.24 – 2.98)

** Data from Figure S5 page 35 of supplementary appendix of CGHFB 2019*

Oestrogen-progestogen combined, past users (aged 40 to 44 at first use of HRT)

Outcome – incidence of breast cancer	HRT users vs HRT never-users, 1-4 years,
Past use, duration <1 year use Relative risk/95% CI	1.37 (0.89 – 2.10)
Past use, duration 1-4 years use Relative risk/95% CI	1.27 (1.00 – 1.61)
Past use, duration 5-9 years use	1.19 (0.98 – 1.44)

Outcome – incidence of breast cancer	HRT users vs HRT never-users, 1-4 years,
Relative risk/95% CI	
Past use, duration over 10 years use Relative risk/95% CI	1.24 (1.08 – 1.42)

** Data from Figure S5 page 35 of supplementary appendix of CGHFB 2019*

Oestrogen-only - current users (aged 40 to 44 at first use of HRT)*

Outcome – incidence of breast cancer	HRT users vs HRT never-users
Current use, Duration <1 year use Relative risk/95% CI	1.29 (0.32 – 5.29)
Current use, duration 1-4 years Relative risk/95% CI	1.10 (0.78 – 1.56)
Current use, duration 5-9 years Relative risk/95% CI	1.24 (1.00 – 1.54)
Current use, duration 10-14 years Relative risk/95% CI	1.41 (1.24 – 1.60)
Current use, duration of use 15 or more years Relative risk/95% CI	1.69 (1.54 – 1.86)

** Data from Figure S5 page 35 of supplementary appendix of CGHFB 2019*

Oestrogen-only, past users (aged 40 to 44 at first use of HRT)*

Outcome – incidence of breast cancer	HRT users vs HRT never-users
Past use, Duration <1 year use Relative risk/95% CI	1.14 (0.86 – 1.52)
Past use, Duration 1-4 years use Relative risk/95% CI	1.13 (0.94 – 1.35)
Duration 5-9 years use Relative risk/95% CI	1.07 (0.90 – 1.28)
Duration over 10 years use Relative risk/95% CI	1.28 (1.16 – 1.42)

** Data from Figure S5 page 35 of supplementary appendix of CGHFB 2019*

Critical appraisal - CASP Critical appraisal checklist for IPD meta-analysis - 2.2 breast cancer

Section	Question	Answer
Is the IPD meta-analysis part of a systematic review?	Does it have a clear research question qualified by explicit eligibility criteria?	Yes (*eligibility criteria clearly reported*)
	Does it have a systematic and comprehensive search strategy for identifying trials?	Yes (*strategy reported in supplementary information*)
	Does it have a consistent approach to data collection?	Yes (*systematic methods for data collection used*)
	Does it assess the “quality” or risk of bias of included trials?	Yes (*no details reported*)
	Are all the methods prespecified in a protocol?	Yes (*draft protocol circulated to collaborators, no further details reported*)

Section	Question	Answer
	Has the protocol been registered or otherwise made available?	Not reported
Were all eligible trials identified?	Were fully published trials identified?	Yes
	Were trials published in the grey literature identified?	No (*grey literature was searched for but not included*)
	Were unpublished trials identified?	Yes
Were IPD obtained for most trials?	Were IPD obtained for a large proportion of the eligible trials?	Yes (*98% of eligible trials included*)
	Was an assessment of the potential impact of missing trials undertaken?	Not reported
	Were the reasons for not obtaining IPD provided?	Yes (*1 study excluded because individual data were not available*)
Was the integrity of the IPD checked?	Were the data checked for missing, invalid out-of-range, or inconsistent items?	Yes (*checked via correspondence with investigators*)
	Were there any discrepancies with the trial report (if available)?	Not reported
	Were any issues queried and, if possible, resolved?	Not reported
Were the analyses prespecified in detail?	Were the detailed analysis methods included in a protocol or analysis plan?	Not reported
	Were the outcomes and methods for analysing the effects of interventions, quantifying and accounting for heterogeneity, and assessing risk of bias	Yes (*details of methods provided in supplementary information*)

Section	Question	Answer
	included?	
Was the risk of bias of included trials assessed?	Were the randomisation, allocation concealment, and blinding assessed?	Not applicable
	Were the IPD checked to ensure all (or most) randomised participants were included?	Not applicable
	Were all relevant outcomes included?	Yes
	Was the quality of time-to-event-outcome data checked?	Not applicable
Were the methods of analysis appropriate?	Were the methods of assessing the overall effects of interventions appropriate?	Yes
	Did researchers stratify or account for clustering of participants within trials using either a one- or two-stage approach to meta-analysis?	Not applicable
	Was the choice of one- or two-stage analysis specified in advance and/or results for both approaches provided?	Not applicable
	Were the methods of assessing whether effects of interventions varied by trial characteristics appropriate?	Yes (*relevant sensitivity analyses were conducted*)
	Did researchers compare treatment effects between subgroups of trials or use meta-regression to assess whether the overall treatment effect varied in relation to trial characteristics?	Not reported

Section	Question	Answer
	Were the methods of assessing whether effects of interventions vary by participant characteristics appropriate?	Yes (*relevant sensitivity analyses were conducted*)
	Did researchers estimate an interaction separately for each trial and combine these across trials in a two-stage fixed effect or random effects meta-analysis? Or;	Not applicable
	Did researchers incorporate one or more a treatment by participant covariate interaction terms in a regression model, whilst also accounting for clustering of participant, separating out this individual participant-level interaction from any trial-level interactions?	Not applicable
	If there was no evidence of a differential effect by trial or participant characteristic, was emphasis placed on the overall result?	Not applicable
	Were exploratory analyses highlighted as such?	Not applicable
Does any report of the results adhere to the Preferred Reporting Items for a Systematic review and Meta-analysis of IPD (The PRISMA-IPD Statement)?		Yes (*all results are reported in full with effect sizes and confidence intervals reported for each meta-analysis*)

1
2

Appendix E Forest plots

Forest plots for review question: 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 and loss of muscle mass and strength?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE and/or GRADE-CERQual tables (or other full modified GRADE tables)

GRADE tables for review question: 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 and loss of muscle mass and strength?

See Appendix L for absolute risk tables.

Table 5: Comparison 1: Oestrogen-progestogen combined versus no HRT

Quality assessment							No of cases		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Oestrogen-progestogen versus no HRT	Control	Relative (95% CI)	Absolute[1]		
Incidence of invasive breast cancer												
Current HRT users – by years of use (age of first HRT use 40 to 44)												
Duration <1 year												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1	NR	RR 0.68 (0.09 – 5.33)	-	LOW	CRITICAL
Duration 1-4 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	37	NR	RR 1.74 (1.16 – 2.61)	-	MODERATE	CRITICAL
Duration 5-9 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	NR	RR 2.18 (1.74 – 2.74)		HIGH	CRITICAL
Duration 10-14 years												
1 (CGHFB	observational	no serious	no serious	no serious	no serious	none	246	NR	RR 2.26 (1.95 –		HIGH	CRITICAL

Quality assessment							No of cases		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Oestrogen-progestogen versus no HRT	Control	Relative (95% CI)	Absolute[1]		
2019)	studies	risk of bias	inconsistency	indirectness	imprecision				2.63)			
Duration 15+ years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	283	NR	RR 2.58 (2.24 – 2.98)		HIGH	CRITICAL
Past HRT users (age of first HRT use 40 to 44)												
Duration <1 year												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	27	NR	RR 1.37 (0.89 – 2.10)	-	MODERATE	CRITICAL
Duration 1-4 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	86	NR	RR 1.27 (1.00 – 1.61)	-	MODERATE	CRITICAL
Duration 5-9 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	133	NR	RR 1.19 (0.98 – 1.44)	-	MODERATE	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	264	NR	RR 1.24 (1.08 – 1.42)	-	MODERATE	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; NR: not reported; RR: relative risk
1. See Appendix L for absolute risk tables
2. 95% CI crosses 2 MIDs
3. 95% CI crosses 1 MID

Table 6: Comparison 2: Oestrogen-only versus no HRT

Quality assessment	No of cases	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only versus no HRT	Control	Relative (95% CI)	Absolute[1]		
Incidence of invasive breast cancer												
Current HRT users – by years of use (age of first HRT use 40 to 44)												
Duration <1 year												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4	NR	RR 1.29 (0.32 – 5.29)	-	LOW	CRITICAL
Duration 1-4 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	49	NR	RR 1.10 (0.78 – 1.56)	-	LOW	CRITICAL
Duration 5-9 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	113	NR	RR 1.24 (1.00 – 1.54)	-	MODERATE	CRITICAL
Duration 10-14 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	324	NR	RR 1.41 (1.24 – 1.60)	-	HIGH	CRITICAL
Duration 15+ years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	576	NR	RR 1.69 (1.54 – 1.86)	-	HIGH	CRITICAL
Past HRT users (age of first HRT use 40 to 44)												
Duration <1 year												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	62	NR	RR 1.14 (0.86 – 1.52)	-	MODERATE	CRITICAL
Duration 1-4 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	145	NR	RR 1.13 (0.94 – 1.35)	-	MODERATE	CRITICAL

Quality assessment							No of cases		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only versus no HRT	Control	Relative (95% CI)	Absolute[1]		
Duration 5-9 years												
CGHFB 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	155	NR	RR 1.07 (0.90 – 1.28)	-	MODERATE	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	466	NR	RR 1.28 (1.16 – 1.42)		MODERATE	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; NR: not reported; RR: relative risk
1. See Appendix L for absolute risk tables
2. 95% CI crosses 2 MIDs
3. 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: 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 and loss of muscle mass and strength?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: 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 and loss of muscle mass and strength?

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 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 and loss of muscle mass and strength?

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 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 and loss of muscle mass and strength?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Abdi, Fatemeh, Mobedi, Hamid, Bayat, Farhad et al. (2017) The Effects of Transdermal Estrogen Delivery on Bone Mineral Density in Postmenopausal Women: A Meta-analysis. Iranian journal of pharmaceutical research : IJPR 16(1): 380-389	- Population - study does not report results for women aged 40 - 45 years
Al Kadri, Hanan, Hassan, Samar, Al-Fozan, Haya M et al. (2009) Hormone therapy for endometriosis and surgical menopause. The Cochrane database of systematic reviews: cd005997	- Population - study does not report results for women aged 40 - 45 years - Comparison - not placebo or no HRT
Alver, Kari, Sogaard, Anne J, Falch, Jan A et al. (2007) The Oslo Health Study: Is bone mineral density higher in affluent areas?. International journal for equity in health 6: 19	- Intervention- not relevant to this review protocol - Does not address the impact of HRT
Anagnostis, P., Christou, K., Artzouchaltzi, A.-M. et al. (2019) Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: A systematic review and meta-analysis. European Journal of Endocrinology 180(1): 41-50	- Intervention- oestrogen-only and combined HRT not reported separately - Comparison - not placebo or no HRT
Anagnostis, Panagiotis, Theocharis, Patroklos, Lallas, Konstantinos et al. (2020) Early menopause is associated with increased risk of arterial hypertension: A systematic review and meta-analysis. Maturitas 135: 74-79	- Intervention- oestrogen-only and combined HRT not reported separately - Comparison - not placebo or no HRT
Barrionuevo, Patricia, Kapoor, Ekta, Asi, Noor et al. (2019) Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. The Journal of clinical endocrinology and metabolism 104(5): 1623-1630	- Population - study does not report results for women aged 40 - 45 years
Bove, Riley, Secor, Elizabeth, Chibnik, Lori B et al. (2014) Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 82(3): 222-9	- Intervention- oestrogen-only & combined HRT not reported separately - Population - study does not report results for women aged 40 - 45 years
Cartwright B, Robinson J, Seed PT et al. (2016) Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. The Journal of clinical endocrinology and metabolism 101(9): 3497-3505	- Population - study does not report results for women aged 40 - 45 years - Mean age in HRT & no HRT groups was 40 years (range 34 to 43)

Study	Code [Reason]
Duan, Lei, Xu, Xinxin, Koebnick, Corinna et al. (2012) Bilateral oophorectomy is not associated with increased mortality: the California Teachers Study. Fertility and sterility 97(1): 111-7	- Population - study does not report results for women aged 40 - 45 years - Intervention- oestrogen-only and combined HRT not reported separately
Ewertz, M, Mellemkjaer, L, Poulsen, A H et al. (2005) Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. British journal of cancer 92(7): 1293-7	- Intervention- oestrogen-only & combined HRT not reported separately
Field, C S, Ory, S J, Wahner, H W et al. (1993) Preventive effects of transdermal 17 beta-estradiol on osteoporotic changes after surgical menopause: a two-year placebo-controlled trial. American journal of obstetrics and gynecology 168(1pt1): 114-21	- Population - study does not report results for women aged 40 - 45 years - Mean age > 45 years
Gatta, Luke A; Jiang, Xuezhi; Schnatz, Peter F (2015) Hormone therapy in women with primary ovarian insufficiency or early menopause. Menopause (New York, N.Y.) 22(9): 923-5	- Study design - not a systematic review, randomised controlled trial, or observational study
Gong, D., Sun, J., Zhou, Y. et al. (2016) Early age at natural menopause and risk of cardiovascular and all-cause mortality: A meta-analysis of prospective observational studies. International Journal of Cardiology 203: 115-119	- Comparison - not placebo or no HRT - Intervention- oestrogen-only and combined HRT not reported separately
Honigberg, Michael C, Zekavat, Seyedeh Maryam, Aragam, Krishna et al. (2019) Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. JAMA 322(24): 2411-2421	- Population - study does not report results for women aged 40 - 45 years - Intervention- oestrogen-only and combined HRT not reported separately
Javed, Ayesha A, Mayhew, Alexandra J, Shea, Alison K et al. (2019) Association Between Hormone Therapy and Muscle Mass in Postmenopausal Women: A Systematic Review and Meta-analysis. JAMA network open 2(8): e1910154	- Population - study does not report results for women aged 40 - 45 years
Lin, Shih-Yin, Hung, Min-Chih, Chang, Shih-Fu et al. (2021) Efficacy and Safety of Postmenopausal Osteoporosis Treatments: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Journal of clinical medicine 10(14)	- Population - study does not report results for women aged 40 - 45 years
Lindh-Astrand, L, Hoffmann, M, Jarvstrat, L et al. (2015) Hormone therapy might be underutilized in women with early menopause. Human reproduction (Oxford, England) 30(4): 848-52	- Outcomes - reported outcomes do not match the review protocols
Liu, S L and Lebrun, C M (2006) Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. British journal of sports medicine 40(1): 11-24	- Intervention- not relevant to this review protocol
Lobo, Rogerio A (2004) Evaluation of cardiovascular event rates with hormone therapy in healthy, early postmenopausal women: results from 2 large clinical trials. Archives of internal medicine 164(5): 482-4	- Population - study does not report results for women aged 40 - 45 years
Lokkegaard, E, Jovanovic, Z, Heitmann, B L et al. (2006) The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. Maturitas 53(2): 226-33	- Intervention- oestrogen-only and combined HRT not reported separately
Maki, P M, Gast, M J, Vieweg, A J et al. (2007) Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. Neurology 69(13): 1322-30	- Population - study does not report results for women aged 40 - 45 years
Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen et al. (2017) Long-term hormone therapy for perimenopausal and	- Population - study does not report results for women aged

Study	Code [Reason]
postmenopausal women. The Cochrane database of systematic reviews 1: cd004143	40 - 45 years
Mittal, Monica, Chitongo, Paradzai, Supramaniam, Prasanna Raj et al. (2022) The effect of micronized progesterone and medroxyprogesterone acetate in combination with transdermal estradiol on hemostatic biomarkers in postmenopausal women diagnosed with POI and early menopause: a randomized trial. Menopause (New York, N.Y.) 29(5): 580-589	- Comparison - not placebo or no HRT
Mittal, Monica, McEniery, Carmel, Supramaniam, Prasanna Raj et al. (2022) Impact of micronised progesterone and medroxyprogesterone acetate in combination with transdermal oestradiol on cardiovascular markers in women diagnosed with premature ovarian insufficiency or an early menopause: a randomised pilot trial. Maturitas 161: 18-26	- Comparison - not placebo or no HRT
Moberg, Louise, Hamrefors, Viktor, Fedorowski, Artur et al. (2022) Early menopause and weight loss are significant factors associated with risk of future fracture in middle-aged women. BMC musculoskeletal disorders 23(1): 779	- Outcomes - reported outcomes do not match the review protocols
Muka, Taulant, Oliver-Williams, Clare, Kunutsor, Setor et al. (2016) Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 1(7): 767-776	- Intervention- oestrogen-only and combined HRT not reported separately - Comparison - not placebo or no HRT
Okoth, Kelvin, Chandan, Joht Singh, Marshall, Tom et al. (2020) Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. BMJ (Clinical research ed.) 371: m3502	- Intervention- not relevant to this review protocol
Orcesi Pedro, A (2018) Update on hormone therapy and osteoporosis prevention. Osteoporosis international conference18thworldconferenceonosteoporosisdegenerativedisease andmusculoskeletaldisorderswcoiofesceo2018poland29(1supplement1): S122-S123	- Conference abstract
Pal, L, Morgan, K, Santoro, NF et al. (2022) Cardiometabolic measures and cognition in early menopause - Analysis of baseline data from a randomized controlled trial. Maturitas 162: 58-65	- Population - study does not report results for women aged 40 - 45 years
Pfeifer, Emily C, Crowson, Cynthia S, Amin, Shreyasee et al. (2014) The influence of early menopause on cardiovascular risk in women with rheumatoid arthritis. The Journal of rheumatology 41(7): 1270-5	- Intervention- not relevant to this review protocol
Pines, A, Sturdee, D W, Birkhauser, M H et al. (2008) HRT in the early menopause: scientific evidence and common perceptions. Climacteric : the journal of the International Menopause Society 11(4): 267-72	- Study design - not a systematic review, randomised controlled trial, or observational study
Prior, J C, Seifert-Klauss, V R, Giustini, D et al. (2017) Estrogen-progestin therapy causes a greater increase in spinal bone mineral density than estrogen therapy - a systematic review and meta-analysis of controlled trials with direct randomization. Journal of musculoskeletal & neuronal interactions 17(3): 146-154	- Comparison - not placebo or no HRT
Ran, S Y, Yu, Q, Chen, Y et al. (2017) Prevention of postmenopausal osteoporosis in Chinese women: a 5-year, double-blind, randomized, parallel placebo-controlled study. Climacteric : the journal of the International Menopause Society 20(4): 391-396	- Population - study does not report results for women aged 40 - 45 years
Rivera, Cathleen M, Grossardt, Brandon R, Rhodes, Deborah J et al. (2009) Increased cardiovascular mortality after early bilateral oophorectomy. Menopause (New York, N.Y.) 16(1): 15-23	- Population - study does not report results for women aged 40 - 45 years

Study	Code [Reason]
Rocca, Walter A; Grossardt, Brandon R; Maraganore, Demetrius M (2008) The long-term effects of oophorectomy on cognitive and motor aging are age dependent. Neuro-degenerative diseases 5(34): 257-60	- Intervention- not relevant to this review protocol
Santos Gonzalez, J.E. (2001) Treatment of early menopause. Revista de Iberoamericana de Revisiones en Menopausia 3(2): 15-18	- Cannot obtain full text of article
Shah, D and Nagarajan, N (2014) Premature menopause - Meeting the needs. Post reproductive health 20(2): 62-68	- Study design - not a systematic review, randomised controlled trial, or observational study
Shuster, Lynne T, Rhodes, Deborah J, Gostout, Bobbie S et al. (2010) Premature menopause or early menopause: long-term health consequences. Maturitas 65(2): 161-6	- Intervention- not relevant to this review protocol
Siegelmann-Danieli, Nava, Katzir, Itzhak, Landes, Janet Vesterman et al. (2018) Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective. Breast cancer research and treatment 167(1): 257-262	- Intervention- not relevant to this review protocol
Signorelli, S S, Salvatore, S, Luigi, D et al. (1999) Serum lipids and lipoproteins and carotid artery wall intima-media thickness in a population of menopausal women. Menopause (New York, N.Y.) 6(3): 230-2	- Intervention- not relevant to this review protocol
Stampfer, M J, Colditz, G A, Willett, W C et al. (1991) Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. The New England journal of medicine 325(11): 756-62	- Population - study does not report results for women aged 40 - 45 years - Intervention- oestrogen-only and combined HRT not reported separately
Stampfer, M J, Willett, W C, Colditz, G A et al. (1985) A prospective study of postmenopausal estrogen therapy and coronary heart disease. The New England journal of medicine 313(17): 1044-9	- Intervention- oestrogen-only and combined HRT not reported separately
Stuursma, Annechien, Lanjouw, Lieke, Idema, Demy L et al. (2022) Surgical Menopause and Bilateral Oophorectomy: Effect of Estrogen-Progesterone and Testosterone Replacement Therapy on Psychological Well-being and Sexual Functioning; A Systematic Literature Review. The journal of sexual medicine	- Population - study does not report results for women aged 40 - 45 years
Sullivan, Shannon D, Lehman, Amy, Nathan, Nisha K et al. (2017) Age of menopause and fracture risk in postmenopausal women randomized to calcium + vitamin D, hormone therapy, or the combination: results from the Women's Health Initiative Clinical Trials. Menopause (New York, N.Y.) 24(4): 371-378	- Population - study does not report results for women aged 40 - 45 years
Tao, X-Y, Zuo, A-Z, Wang, J-Q et al. (2016) Effect of primary ovarian insufficiency and early natural menopause on mortality: a meta-analysis. Climacteric 19(1): 27-36	- Comparison - not placebo or no HRT - Intervention- oestrogen-only and combined HRT not reported separately
Xu, Yang, Deng, Kai-Li, Xing, Tian-Fang et al. (2020) Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause (New York, N.Y.) 27(7): 827-835	- Population - study does not report results for women aged 40 - 45 years
Xu, Z., Wang, H., Shi, Y. et al. (2020) Impact of calcium, Vitamin D, vitamin K, oestrogen, isoflavone and exercise on bone mineral density for osteoporosis prevention in postmenopausal women: A network meta-analysis. British Journal of Nutrition 123(1): 84-103	- Duplicate publication

Study	Code [Reason]
Xu, Zhiwei, Chung, Hsin-Fang, Dobson, Annette J et al. (2022) Menopause, hysterectomy, menopausal hormone therapy and cause-specific mortality: cohort study of UK Biobank participants. Human reproduction (Oxford, England) 37(9): 2175-2185	- Intervention- oestrogen-only and combined HRT not reported separately
Yoshida, Yilin, Chen, Zhipeng, Baudier, Robin L et al. (2021) Early Menopause and Cardiovascular Disease Risk in Women With or Without Type 2 Diabetes: A Pooled Analysis of 9,374 Postmenopausal Women. Diabetes care 44(11): 2564-2572	- Intervention- oestrogen-only and combined HRT not reported separately - Comparison - not placebo or no HRT
Zhu, Dongshan, Chung, Hsin-Fang, Dobson, Annette J et al. (2020) Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. Human reproduction (Oxford, England) 35(8): 1933-1943	- Intervention- oestrogen-only and combined HRT not reported separately
Zhu, Dongshan, Chung, Hsin-Fang, Dobson, Annette J et al. (2019) Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. The Lancet. Public health 4(11): e553-e564	- Intervention- oestrogen-only and combined HRT not reported separately - Comparison - not placebo or no HRT
Zurcher, A., Knabben, L., Janka, H. et al. (2022) Influence of the levonorgestrel-releasing intrauterine system on the risk of breast cancer: a systematic review. Archives of Gynecology and Obstetrics	- Intervention- not relevant to this 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 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 and loss of muscle mass and strength?

K.1.1 Research recommendation

What is the effect of either taking or not taking hormone replacement therapy on health outcomes for people with early menopause (aged 40 to 44)?

Why this is important

The relative risks compared to benefits of HRT after early menopause are poorly understood. Early menopause reduces the risk of breast cancer, endometrial and ovarian cancer and taking HRT may reduce these benefits. On the other hand, some guidelines (e.g. ESHRE) suggested possibly increased risk for cardiovascular disease, osteoporosis and dementia without HRT.

Rationale for research recommendation

Table 8: Research recommendation rationale

Importance to 'patients' or the population	The long-term health consequences of HRT on women with early menopause are poorly understood. HRT may be offered for vasomotor symptoms but whether it reduces the risk of chronic disease such as cardiovascular disease and osteoporosis is uncertain. The optimum dose and duration of HRT use is also uncertain.
Relevance to NICE guidance	This is limited evidence to guide the clinical care of women with early menopause. In particular, the relative risks vs benefit of HRT. This information is essential to inform future updates of key recommendations of this guideline.
Relevance to the NHS	The outcome would affect whether and for how long HRT is recommended following early menopause. If HRT was protective against long-term disease such as fracture or CVD, this could reduce the amount of treatment needed for fractures or cardiovascular disease.
National priorities	High – Menopause, including HRT use, is part of Department of Health & Social Care's Women's Health Strategy for England.
Current evidence base	There is very little evidence to inform the long-term health consequence of HRT on women with early menopause.
Equality considerations	Black women are known to start menopause transition earlier than other racial and ethnic groups. Further research would address equality considerations particularly in the following groups, people: • with disabilities

	• from diverse races and ethnicities • from diverse socio-economic backgrounds

HRT: Hormone replacement therapy

Modified PICO table

Table 9: Research recommendation modified PICO table

Population	Women, trans men and non-binary people registered female at birth with early menopause aged 40 to 44. The committee would recommend further research that would address equality considerations (see the equality impact assessment form) particularly in the following groups, people: • with disabilities • across a range of race / ethnicities • from a wider range of socio-economic backgrounds

Intervention	HRT*
	• Oestrogen-only
	• Combined oestrogen and progestogen
	  ○ Sequential combined
	  ○ Continuous combined
	  ○ Any combined
	* Regulated micronised progesterone are included but compounded micronised progesterone are excluded.

Comparator	• Placebo treatment • No HRT
Outcome	• Death from any cause • Venous thromboembolism • Cardiovascular disease • Type 2 diabetes: • Osteoporosis: • Vertebral fracture • Hip fracture • Loss of muscle mass and strength and function: • Falls • Incidence of breast cancer • Incidence of endometrial cancer • Incidence of ovarian cancer • Dementia
Study design	• 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.
Timeframe	Long-term (40 years)
Additional information	None

HRT: Hormone replacement therapy

Additionally, there are overarching research recommendations related to all health outcomes addressed in this guideline update (including endometrial cancer), 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 table and calculations

Absolute risk tables and calculations for review question: 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 and loss of muscle mass and strength?

Table 10: Number of breast cancer cases with no use, current use and past use of combined HRT in people with early menopause (age 40-44) who, if they used it, started HRT at 40 and used it for 10 years

	40-44 years old	45-49 years old	50-54 years old	55-59 years old	40-59 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	5	8	10	10	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who started HRT at 40 and used it for 10 years	8 (current user)	17 (current user)	12 (past user)	13 (past user)	Not applicable
Cumulative number of breast cancer cases over a 20-year period per 1000 people who never used HRT	Not applicable	Not applicable	Not applicable	Not applicable	33
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 40 and used it for 10 years	Not applicable	Not applicable	Not applicable	Not applicable	51

Table 11: Number of breast cancer cases with no use, current use and past use of oestrogen-only HRT in people with early menopause (age 40-44) who, if they used it, started HRT at 40 and used it for 10 years

	40-44 years old	45-49 years old	50-54 years old	55-59 years old	40-59 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	5	8	10	10	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who started HRT at 40 and used it for 10 years	5 (current user)	10 (current user)	13 (past user)	13 (past user)	Not applicable
Cumulative number of breast cancer cases over a 20-year period per 1000 people who never used HRT	Not applicable	Not applicable	Not applicable	Not applicable	33
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 40 and used it for 10 years	Not applicable	Not applicable	Not applicable	Not applicable	41

Calculations

Absolute risks for HRT users were calculated by applying the relevant risk ratios to the risk of breast cancer in never users.

The rate of breast cancer incidence in never users of HRT was calculated by solving the following formula:

Incidence among all women in a given age range = [proportion of women who are current users × (RRcurrent × β)] + [proportion of never users × β]

Where:

β = risk of breast cancer in never users

RRcurrent = The average breast cancer relative risk for HRT users versus never users [RR (current vs never users)] in the general population is taken from the risks in supplementary figure 3 in CGHFBC 2019, assuming ¼ of HRT users use oestrogen-only and ¾ use combined HRT. This gives an average RR of 1.8.

The proportion of women using HRT in each age band is estimated using NHS HRT data on Hormone Replacement Therapy in 2017 and dividing by the ONS census population figures for women in that age band for 2017 × the proportion who are post-menopausal).

The breast cancer 5 year incidence for all women in each age band is taken from ONS breast cancer registration statistics for 2017.

The breast cancer incidence rate for women with early menopause β, is estimated using the proportions of HRT users and never users in each age band, RR (current vs never users) and the RRs associated with age of menopause from CGHFBC 2012, as below:

- Incidence among all women in age range 40-44=
    - proportion of never users with age@meno 40-44 x β +
    - proportion of never users with age@meno<40 x RR (meno <40 vs 40-44) x β +
    - proportion of never users with age@meno>=45 x RR (meno>=45 vs 40-44) +
    - proportion of users with age@meno 40-44 x RR (current vs never users) x β +
    - proportion of users with age@meno <40 x RR (meno <40 vs 40-44) x RR (current vs never users)

The HRT associated risks with use from 40 to 49 in women with early menopause are then estimated separately using RRs for oestrogen-only and combined HRT use from supplementary table 5 (page 35) of CGHFBC 2019. Specifically, the RRs for 40-44 are for current users duration 1-4 years, the RRs for users 45-59 are for current users duration 5-9 years and the RRs for both age 50-54 and 55 to 59 are past users duration 10+ years.

The proportions of postmenopausal women by age are taken from Mishra 2017.

Please see Supplement 19 for calculations.

References

Mishra 2017

Mishra GD, Pandeya N, Dobson AJ, Chung HF, Anderson D, Kuh D, Sandin S, Giles GG, Bruinsma F, Hayashi K, Lee JS, Mizunuma H, Cade JE, Burley V, Greenwood DC, Goodman A, Simonsen MK, Adami HO, Demakakos P, Weiderpass E. Early menarche, nulliparity and the risk for premature and early natural menopause. Hum Reprod. 2017 Mar 1;32(3):679-686. doi: 10.1093/humrep/dew350. PMID: 28119483; PMCID: PMC5850221

CGHFBC 2012

Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141-51. doi: 10.1016/S1470-2045(12)70425-4. Epub 2012 Oct 17. PMID: 23084519; PMCID: PMC3488186.

CGHFBC 2019

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168. doi: 10.1016/S0140-6736(19)31709-X. Epub 2019 Aug 29. PMID: 31474332; PMCID: PMC6891893.