National Institute for Health and Care Excellence

Draft for consultation

Menopause (update)

[D] Breast cancer

NICE guideline number tbc

Evidence review underpinning recommendations 1.4.1, 1.4.2, 1.5.6 and 1.6.1 (except the first 2 bullet points) and the statements related to breast cancer in tables 1 and 2 as well as research recommendation 2 in the NICE guideline

November 2023

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This evidence review was developed by NICE

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Breast cancer

Review question

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

Introduction

Hormone replacement therapy (HRT) may be used for the management of menopausal symptoms. The effects of HRT on the risk of breast cancer incidence, and mortality from breast cancer are unknown. This review aims to look at the incidence of invasive breast cancer, and mortality from breast cancer in users of HRT, compared to those who do not take HRT. This review also aims to look at whether the incidence of breast cancer or mortality from breast cancer is different depending on the duration of use, whether you are a current or past user, the type of HRT used, and a number of other characteristics such as ethnicity or socioeconomic status.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

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

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

Comparison	• Placebo treatment • No HRT
Outcome	**Critical** • Incidence of invasive breast cancer • Mortality from breast cancer **Important** • None

HRT: hormone replacement therapy

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

Six publications were included for this review, two retrospective cohort studies (Brusselaers 2018; Chen 2002), one randomised controlled trial (RCT (Chlebowski 2020), one prospective studies (Fournier 2014) as well as one individual patient (IPD) meta-analysis of 24 observational studies and six RCTs (CGHFB 2019). A published correspondence with follow-up data from the Million Women Study was also included (Beral 2019).

The included studies are summarised in Table 2.

Four studies compared oestrogen-only to no hormone replacement therapy (HRT) or placebo (Brusselaers 2018; CGHFB 2019; Chen 2002; Chlebowski 2020). Five studies compared combined oestrogen plus progestogens to no HRT or placebo (Brusselaers 2018; CGHFB 2019; Chen 2002; Chlebowski 2020; Fournier 2014). One prospective cohort study (Fournier 2014) was included in the IPD meta-analysis (CGHFB 2019), but data on one sub-group was included separately in this review as further participants were analysed in the publication. One published correspondence for the Million Women Study (Beral 2019) compared oestrogen-only to no HRT, and oestrogen plus progestogen to no HRT.

The studies were from France, Sweden, United Kingdom and United States. The individual participant data meta-analysis included studies from Europe and North America.

The included studies are summarised in Table 2.

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Beral 2019 Prospective cohort study United Kingdom	N=907162 postmenopausal women Mean age, years (SD): 56 (5)	• Oestrogen-only HRT • Oestrogen plus progestogen HRT	• No HRT use	• Mortality from breast cancer	Published correspondence related to follow-up data from the Million Women Study (*Green J, Reeves GK, Floud S, Barnes I, Cairns BJ, Gathani T, Pirie K, Sweetland S, Yang TO, Beral V; Million Women Study Collaborators. Cohort Profile: the Million Women Study.*

Study	Population	Intervention	Comparison	Outcomes	Comments
					(2019) Int J Epidemiol 48(1):28-29e)
Brusselaers 2018 Retrospective cohort study Sweden	N=1160351 women Age: 40+ years Mean age, years (SD): not reported	• Oestrogen-only HRT • Oestrogen plus progestogen HRT	• No HRT use	• Incidence of breast cancer Subgroups: • Current HRT use • Mode of administration • Constituent of oestrogen • Frequency of progestogen	Confounders adjusted for: • hysterectomy • ever parous • thrombotic events • year of birth • smoking-related diseases • alcohol-related diseases • obesity • diabetes mellitus • osteoporosis
Chen 2002 Retrospective cohort study United States	N= 1104 women Age: 50-74 years Mean age, years (SD): not reported	• Oestrogen-only HRT • Oestrogen plus progestogen HRT	• No HRT use	• Incidence of breast cancer Subgroups • Current/past HRT use • Continuous combined • Sequential combined	Confounders adjusted for: • age at: ○ menarche ○ reference ○ menopause ○ first birth • type of menopause • parity • family history of breast cancer • years of oral contraceptive use • measures of screening • mammography before diagnosis
Chlebowski 2020 Randomised controlled trial United States	Conjugated equine oestrogen (CEE) only: N=10739 Age, mean (SD): CEE: 63.6 (7.3)	• Oestrogen (CEE) only HRT • Oestrogen (CEE) plus progestogen (MPA) HRT	• Placebo	• Incidence of breast cancer Subgroups: • Ethnicity • Family history	Main analyses included in CGHFB but mortality. Further subgroups included and 20.7 years mortality data used.

Study	Population	Intervention	Comparison	Outcomes	Comments
	Placebo: 63.6 (7.3) Conjugated equine oestrogen plus medroxyprogesterone acetate (CEE + MPA): N=16608 Age, mean (SD): CEE + MPA: 63.2 (7.1) Placebo: 63.3 (7.1)			• Mortality from breast cancer	
Collaborative Group on Hormonal Factors in Breast (CGHFB) 2019 Meta-analysis of prospective cohort studies using individual participant data (nested case control)) Meta-analysis of RCTs	K=24 prospective cohort studies N=490994 women Mean age at diagnosis, years (SD): 65 (7) K= 6 RCTs N=13165 women (oestrogen-only studies) N=24919 women (oestrogen plus progestogen studies) Mean age at entry, years: 63.5 (SD not reported)	• 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 • Time since menopause and first use • Mode of administration • Constituent of oestrogen • Constituent of progestogen • Frequency of progestogen • Family history of breast cancer • Ethnicity • Socio-economic deprivation	Confounders adjusted for: • family history (first degree relative with breast cancer • alcohol consumption • reproductive history • age at menopause
Fournier 2014 Prospective cohort study France	N=79353 Mean age at end of follow-up, years, (SD): Never user:	• Oestrogen + progesterone / dydrogesterone	• No HRT use	• Incidence of breast cancer Subgroups:	Cohort included in CGHFB, therefore only subgroup information extracted. There will be some

Study	Population	Intervention	Comparison	Outcomes	Comments
	67.1 (7.8) Past user: 67.0 (5.8) Current user: 63.1 (5.5)			• Constituent of progestogen	overlap with CGHFB but additional cases included in this publication. Data not meta-analysed with CGHFB.

CEE: conjugated equine oestrogen; CGHFB: Collaborative Group On Hormonal Factors in Breast; HRT: hormone replacement therapy; MPA: medroxyprogesterone acetate; RCT: randomised controlled trial

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

Summary of the evidence

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

Any combined oestrogen and progestogen versus no HRT

Users of combined oestrogen and progestogen were compared to non-users of HRT in three observational studies for the outcome incidence of breast cancer. Most of the evidence was rated moderate to high quality. The evidence showed that there was an overall increased risk of breast cancer incidence in those using combined oestrogen and progestogen, compared to non-users. However, there were differences in risk depending on whether users were current or past HRT users, and on the duration of HRT use.

In current users of combined HRT, there was an increased risk of invasive breast cancer in users of less than 1 year's duration up to 15 or more years duration, compared to non-users, and this increased risk was greater with longer durations of use. Most of the evidence was of high quality, with some at very low to moderate. In past users of HRT, there was no difference in risk, compared to non-users, in those with less than 1 year duration of past use, but there remained some increased risk of invasive breast cancer for longer durations of past use, which increased with increasing duration of past use. The evidence was of moderate to high quality.

The evidence was also stratified by oestrogenic and progestogenic constituent, time interval between menopause and first use of HRT, age at first use of HRT, mode of administration, family history of breast cancer, ethnicity, and education. Most of the evidence for the subgroup analysis was rated high quality, with only some at low to moderate quality. Most of the evidence showed that users of combined oestrogen and progestogen had an increased risk of invasive breast cancer compared to non-users regardless of subgroup, with only a few exceptions for age at first use. When stratified by age at first use, high quality evidence showed the risk was increased in all ages from 40 years up to 69 years. Low quality evidence showed a reduced risk when the age at first used was less than 60 years. Low to moderate quality evidence showed that both oral and transdermal modes of administration of oestrogen in the combined preparations, had an increased risk of breast cancer, and that oral oestrogen preparations had a greater risk than transdermal oestradiol.

Moderate quality evidence from one observational study also showed that current users of combined oestrogen and progestogen had an increased rate of mortality from breast cancer, compared to non-users.

Continuous combined oestrogen and progestogen versus no HRT, or placebo

Low to moderate quality evidence from three observational studies showed that there was an increased risk of breast cancer in current users of continuous combined HRT when duration of use was between 1 to 14 years of use, but no differences with use of less than 1 year.

There was also no difference in breast cancer risk in past users of less than 5 years since they last used, when duration of use was between 1 to 4 years.

When compared to placebo in randomised controlled trials, moderate quality evidence showed an increased risk for incidence of invasive breast cancer for users of continuous combined oestrogen and progestogen. Subgroup analysis by ethnicity showed an increased risk of breast cancer for users of continuous combined oestrogen and progestogen when compared to placebo in those of non-Hispanic white ethnicity, but no difference between groups for non-Hispanic black ethnicity. The evidence was of low to moderate quality. Subgroup analysis by family history of breast cancer showed an increased risk of breast cancer for users of continuous combined oestrogen and progestogen when compared to placebo in those with and without a first-degree relative with breast cancer. The evidence was of moderate quality.

There was no difference between users and non-users in the rate of mortality from breast cancer.

Sequential combined oestrogen and progestogen versus no HRT

Low to high quality evidence from 3 observational studies showed there was no difference in risk of breast cancer in current users of sequential combined HRT when duration of use was between 1 to 4 years of use, but an increased risk of breast cancer in current users who used for 5 to 14 years. There was also no difference in past users of less than 5 years since they last used, when duration of use was between 1 to 4 years.

Oestrogen-only HRT versus no HRT

Users of oestrogen-only HRT were compared to non-users of HRT across three observational studies. Most of the evidence was of moderate quality but ranged from low to high. The evidence showed that there was an overall increased risk of incidence of invasive breast cancer in those using oestrogen-only HRT, compared to non-users. However, there were differences in risk depending on whether users were current or past oestrogen-only HRT users, and on how long they had used oestrogen-only HRT for.

In current users of oestrogen-only HRT, moderate quality evidence showed there was no difference in the risk of invasive breast cancer when duration of use was less than 1 year. However, for durations of 1 year up to 15 or more years of current use of oestrogen-only HRT, low to high quality evidence showed there was an increased risk of invasive breast cancer compared to non-users, which was greater for longer durations of use. In past users of oestrogen-only HRT, there remained some increase in the risk of invasive breast cancer compared to non-users. This increased risk in past users was greater for longer durations of past use, and was evident in those who stopped use within the last 5 years, 5-9 years ago and 10 or more years ago if they had used for 10 years or more. The quality of the evidence ranged from very low to high, with most of the evidence of moderate to high quality.

The evidence was also stratified by constituent, age at first use, time since the menopause, age at first HRT use, mode of administration, family history of breast cancer, ethnicity, and education. Most of the evidence showed that users of oestrogen-only HRT had an increased risk of invasive breast cancer compared to non-users regardless of subgroup, with only a few exceptions for constituent and age at first use. When stratified by constituent, low quality evidence showed a reduction in breast cancer incidence in oestriol HRT users, but moderate quality evidence from another study showed that there was no difference in breast cancer incidence in oestriol HRT users. Moderate quality evidence also showed that there was no difference in breast cancer risk in estropipate HRT users. Moderate to high quality evidence showed an increased risk in breast cancer incidence in for oestradiol, equine oestrogens, and conjugated oestrogen HRT users. When stratified by age at first use, only some of the evidence of moderate quality, showed a reduction in the risk of breast cancer incidence when HRT was started at less than 60 years, whereas most of the evidence, rated moderate to

high, showed an increased risk of breast cancer incidence in HRT users. Some of the evidence of moderate quality also showed an increased risk in breast cancer incidence when HRT was started between 60-69 years, whereas evidence from another study showed no difference in risk between HRT users and no-HRT.

Low quality evidence also showed that current users of oestrogen-only HRT had an increased risk of mortality from breast cancer, compared to non-users.

Oestrogen-only HRT versus placebo

Users of oestrogen-only HRT were also compared to placebo in randomised controlled trials of low to moderate quality The evidence showed that users had a lower risk of incidence of invasive breast cancer compared to placebo, as well as a lower risk of mortality from breast cancer.

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 J.

Summary of included economic evidence

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose incidence of invasive breast cancer and mortality from breast cancer as the critical outcomes for this review. They agreed it was important to find out the risks of incidence and mortality from breast cancer so that women can make informed choices.

The quality of the evidence

The quality of the evidence was rated from low to high, with most of the evidence at moderate to high quality. The evidence was mainly downgraded for concerns around imprecision. Some of the evidence was downgraded for risk of bias due to not adjusting for all appropriate confounders (age at menopause and family history of breast cancer), however most of the evidence made the appropriate adjustments and no concern for residual

confounding. There were also some concerns around deviations for the intended intervention, as prescription registries or women's self-reporting may indicate the use of HRT, but it cannot be fully confirmed that they took the HRT. There were also some concerns around inconsistency for some of the evidence, that could not be explained by subgrouping.

In cases where the outcomes were statistically significant the committee considered the GRADE default imprecision rating and the resulting overall quality rating as being an overly conservative estimate of quality. Statistical significance featured in their discussions as an additional factor during decision-making (see also the 'Guideline recommendations' section in Supplement 1 – Methods).

Please note: Beral 2019 is a correspondence letter with result information only and little information on the cohort. Therefore the critical appraisal of Beral 2019 was done using information from a cohort profile (Green 2019) as this provides details of the study design and methods of the cohort that the data in Beral 2019 originated from .

Benefits and harms

The committee discussed the evidence on the use of hormone replacement therapy and breast cancer incidence and mortality. They discussed that most of the evidence on the risk of breast cancer with HRT was from the individual patient data meta-analysis (from observational studies), but that there was also evidence from randomised controlled trials. The committee discussed that there were inconsistencies between the different confounders that had been adjusted for across the observational studies, in particular smoking status and alcohol intake, but agreed that they were very concerned that there was scope for residual confounding. They discussed that although HRT users different from non-users in terms of smoking status and alcohol intake, whilst these factors are associated with many cancers, they are less strongly associated with breast cancer risk and so they were less concerned about scope for residual confounding for associations of HRT with breast cancer than for other conditions, such as cardiovascular disease (see evidence review C).

Discussing treatment options

Based on experience, the committee emphasised that, to allow people to make an informed choice about treatment options, applying basic principles of care is particularly important when discussing HRT, especially:

- using an individualised approach with discussions about risks and benefits of treatment options and
- tailoring information to the person's age, individual circumstances and potential risk factors.

The committee noted that there are different ways of prescribing HRT (combined versus oestrogen-only, modes of administration, types of hormones, schedule, and dosage and duration) and that clinicians should provide information about the risks and benefits associated with these options.

The committee noted that 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. Based on their expertise and experience, they discussed that the way HRT is prescribed influences these benefits and risks, so it also influences the balance between them. 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.

Taking comorbidities into account

The committee agreed, based on their expertise, that oestrogen can promote the growth and proliferation of certain hormone-sensitive breast cancers. There are also other safety concerns around HRT for people with, or at high risk of, breast cancer. However, the committee agreed that this, as well as some other menopause symptom management, is already covered in the section on menopause symptoms in the NICE guideline on early and locally advanced breast cancer. They noted that this was already cross-referred in an existing recommendation in this guideline, so they did not make any new recommendation on this.

Stopping HRT

The committee agreed, based on their expertise, that HRT could potentially lead to cancer progression or risk of recurrence. They agreed that HRT should be stopped in people who are diagnosed with breast cancer and because of other safety concerns. However, they agreed that this is already covered in the section on menopause symptoms in the NICE guideline on early and locally advanced breast cancer and therefore cross-referred to it.

Any combined oestrogen and progestogen versus no HRT

The committee looked at the evidence for oestrogen and progestogen combined. They discussed that the evidence from observational studies showed that overall, the risk of breast cancer incidence was higher in current users of combined HRT compared to non-users. They discussed the subgroup analysis which showed that the increased risk in current users of HRT differed according to the duration of use. The evidence showed an increased risk in users with durations of less than a year, up to 15 or more years of use, and the increase in risk was greater with longer durations of use. The committee noted that the observational evidence showed, among past users who had used combined HRT for 10 years or more, the risk of breast cancer 10 years or more after stopping use was still increased. The committee looked at the RCT data together with the observational data and agreed that they both showed the same direction of effect. Therefore, the committee made recommendations advising women of the risks of breast cancer incidence associated with combined oestrogen and progestogen use.

The committee also looked at the subgroup analysis by mode of administration. They noted that both oral and transdermal administrations of the oestrogen in the combined preparations were associated with an increased risk in breast cancer. However, they discussed that the oral mode of administration had a greater increase in risk than the transdermal mode of administration, and agreed that it was important to note this in the recommendation as it would allow women to make an informed decision regarding the mode of administration.

Mortality risk with breast cancer

The committee discussed the evidence for mortality from breast cancer associated with HRT use. They discussed that the evidence from observational data showed an increased risk of mortality from breast cancer in users of combined progestogen and oestrogen, and oestrogen-only when compared to non-users. They noted that an increased incidence of breast cancer was in line with an increased risk of mortality from breast cancer because it is unlikely that breast cancer prognosis following HRT use would be any different to breast cancer prognosis with respect to mortality in general. However, the committee also noted when looking at the details of the studies that the overall mortality was low with the increase associated with HRT also being small. It was raised by some members of the committee that the RCT evidence did not show a statistically significant difference for combined progestogen and oestrogen, and a reduced risk for oestrogen-only, and this was from a larger sample size than the observational evidence for mortality. However, since the committee were confident

that the observational evidence showed an increased risk of incidence of breast cancer, they discussed that this would support the observational evidence showing an increased risk of breast cancer mortality. They reached a majority decision to inform women that incidence of breast cancer, and subsequent mortality from breast cancer are both increased with HRT use, but that the mortality increase was very small.

Different preparations of combined HRT (type of progestogen or progesterone)

The committee discussed the evidence around the different types of progestogen constituent, for example the risk of breast cancer with combined HRT depended on the type of progestogen or progesterone and whether micronised progesterone was associated with less breast cancer risk versus synthetic progestogens. They agreed that there was insufficient evidence to suggest that micronised progesterone was associated with a lower risk of breast cancer versus synthetic progestogens, therefore a research recommendation in this area was made.

Continuous combined or sequential combined oestrogen and progestogen versus no HRT, or placebo

Since women who retain their uterus can choose to take HRT as a continuous combined or sequential preparation, the committee discussed the evidence around sequential and continuous use of progestogen in combined hormone replacement therapies. The committee discussed that the evidence showed both sequential and continuous combined preparations were associated with an increased incidence of breast cancer, but this risk was greater with continuous combined vs sequential preparations. They agreed that there was a risk that women may stop taking the progestogen component in order to reduce the risk of breast cancer. The committee discussed that in women with a uterus this would lead to unopposed oestrogen which is associated with an increased risk in incidence of endometrial cancer. Despite these concerns of non-adherence to the prescribed combined HRT preparation, it was decided that people should be made aware of this to make an informed choice.

Impact of ethnicity on breast cancer risk with combined HRT use

The committee looked at the evidence stratified by different ethnic groups. They noted that most of the evidence across all the comparisons showed no differences in the increased risk of incidence of breast cancer between different ethnic groups. They discussed that for continuous combined oestrogen and progestogen versus placebo, the evidence showed a difference in the risk of incidence of breast cancer between different ethnic groups. They discussed that the evidence for non-Hispanic white ethnicity group remained consistent with most of the evidence that showed an increased risk of breast cancer in HRT users compared to no use, but that there seemed to be no difference in risk in non-Hispanic black ethnicity group. The committee discussed their concerns around the small sample size of these subgroups and whether they could be confident that this was a true effect. They discussed using their expert knowledge that there are inequalities with regard to recruitment into trials of hormone replacement therapy, for minority ethnic groups and that this leads to small numbers of women and low quality evidence on the specific effects of hormone replacement therapy in those groups. The committee therefore did not feel confident to make a recommendation based on this evidence but made a research recommendation to address this (see the related section below with details of the research recommendation available in Appendix K of evidence review C).

Oestrogen-only versus no HRT, or placebo

The committee discussed the evidence for the comparison of oestrogen-only HRT users versus non-users, or versus placebo. They first discussed the evidence from the observational studies and noted that, overall, the evidence showed that there was an

increased risk in breast cancer incidence in those taking oestrogen-only HRT compared to non-users. The committee discussed the subgroup analysis that showed that the increased risk in current users of HRT differed according to duration of use. The evidence showed that, compared to non-users, there was an increased risk detectable after 1 to 4 years of use which increased with longer durations of use. They then looked at the evidence for past users of HRT and noted that while past users had an increased risk compared with non-users, this increase was somewhat less than that seen in current users. The increased risk of breast cancer in past users also increased with increasing duration of use. The committee noted that, among past users who had used oestrogen-only HRT for 10 years or more, there was still an increased risk of breast cancer 10 years or more after stopping use. The committee agreed that it was important to make women aware of the increased risk of breast cancer incidence in users of oestrogen-only HRT, and that this risk increased with duration of use, and persisted for 10 years or more after stopping use. The committee acknowledged that the increased risk with oestrogen-only HRT in absolute terms, is still lower than the risk observed with combined HRT.

The committee discussed RCT evidence for this comparison. This evidence was inconsistent with the evidence from the observational studies since it showed a reduced risk in the incidence of breast cancer for oestrogen-only HRT users compared with placebo. The committee discussed that in the observational evidence, the mean age of women when starting HRT was 50 years old, whereas in the RCT evidence the mean age of women when starting HRT was 63 and a greater proportion of women in the RCT compared to the observational studies were overweight or obese (who would already have an increased risk before HRT use). The committee also looked at the evidence from observational studies stratified by the time interval between menopause and first HRT use. They noted that the risk of incidence of breast cancer when there was an interval of 5 or more years, was lower than the risk when there was an interval of less than 5 years between menopause and first use. Based on knowledge they also noted that the increased risk of breast cancer in users of oestrogen-only HRT was relatively lower in those with higher body mass index. Therefore, any increase in risk in oestrogen-only HRT users in the RCT might be expected to be lower than that found in the observational studies. The apparent discrepancy between the findings of the RCT and the observational studies may not be as great as it appears. The committee discussed that the one indication for HRT use in the RCT evidence was for the prevention of cardiovascular disease. They discussed that the scope of this guideline was for women who have menopause symptoms which are most common at the start of menopause. The committee therefore agreed that they would put more weight on the observational evidence as this was more reflective of the target population. They decided that it should be explained to people that there is an increased risk as shown in the observational studies rather than the reduced risk in the RCT evidence.

The committee also looked at the evidence that was stratified by different types of oestrogens and different modes of administration. They agreed that the evidence did not support differences in risk of incidence of breast cancer depending on the type of oestrogen or the mode of administration and agreed that it would be useful for people to know that there is no difference in the increase by type of oestrogen or by mode of administration.

Research recommendation

Despite a lack of evidence relating to transgender men and non-binary people the committee agreed that the evidence was generalisable to those who have never taken gender affirming hormone therapy but were uncertain about transgender people who have taken gender affirming hormone therapy in the past and no evidence was identified for this group. They also noted that there was some evidence for people from minority ethnic family backgrounds. However, this evidence was not conclusive.

They agreed to make research recommendations for these groups to fill this evidence gap. The descriptions of the research recommendations can be found in appendix K of evidence report C.

Cost effectiveness and resource use

No previous economic evidence was identified for this topic.

The recommendations made for this review topic centre around the impact of HRT on the risk of breast cancer. Whilst recommendations in this area will potentially 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 identifying a decreased risk of breast cancer from transdermal HRT compared to oral HRT may encourage more people to opt for the transdermal administration. Transdermal administration is approximately double the cost of oral. The use of transdermal administration is increasing in the NHS and offering women a choice allows for individualised treatment. Transdermal patches will also not be suitable for all people for example those who swim or moisturise their skin regularly. The previous guideline also highlighted an increased risk of stroke for oral compared to transdermal administration so women concerned about future health events or with higher risk factors may already prefer transdermal administration.

Other factors the committee took into account

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

Based on their experience the committee noted that advice needs to be tailored to the woman because it is possible that there are risk factors that she could influence by changing her lifestyle (for example reducing alcohol intake) and that there are also risk factors that they may have but which cannot be changed (for example having a pathogenic genetic variant that increases the risk of breast cancer). Relating this to HRT use the committee acknowledged that people considering HRT need to be aware of these factors because the absolute risks associated with HRT use will be greater in those who have a greater risk of breast cancer to start with. The committee were aware that such factors were listed in other NICE guidelines (see lifestyle-related risk factors in the NICE guideline on early and locally advanced breast cancer or recommendation 1.3.1 NICE's guideline on familial breast cancer) and cross referred to them so that these can be discussed.

The committee discussed the relative risks as well as the absolute numbers per 1000 people, see GRADE tables in Appendix F and absolute numbers for observational evidence in Appendix L (with calculations available in Supplement 19). They recommended that these should be discussed with the person.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1, 1.4.2, 1.5.6 and 1.6.1 (except the first two bullet points) as well as the statements related to breast cancer in tables 1 and 2 as well as research recommendation 2 (on the type of progestogen in HRT and breast,

endometrial cancer or cardiovascular disease) in the NICE guideline. It also supports an overarching recommendation related to trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past (recommendation 1.4.8 – see evidence review C).

The committee also agreed a research recommendation on type of progestogen in HRT and breast, endometrial cancer or cardiovascular disease. See appendix K in evidence review D for the details of this research recommendation.

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.

References – included studies

Beral 2019

Beral, Valerie et al. (2019) Menopausal hormone therapy and 20-year breast cancer mortality. The Lancet 394 (10204): 1139 (published correspondence for data from the Million Women Study)

Brusselaers 2018

Brusselaers, N, Tamimi, R M, Konings, P et al. (2018) Different menopausal hormone regimens and risk of breast cancer. Annals of oncology: official journal of the European Society for Medical Oncology 29(8): 1771-1776

Chen 2002

Chen, Chi-Ling, Weiss, Noel S, Newcomb, Polly et al. (2002) Hormone replacement therapy in relation to breast cancer. JAMA 287(6): 734-41

Chlebowski 2020

Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, Barrington W, Kuller LH, Simon MS, Lane D, Johnson KC, Rohan TE, Gass MLS, Cauley JA, Paskett ED, Sattari M, Prentice RL (2020) Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality during Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 324(4): 369-380

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

Fournier 2014

Fournier, Agnes; Mesrine, Sylvie; Dossus, Laure; Boutron-Ruault, Marie-Christine; Clavel-Chapelon, Francoise; Chabbert-Buffet, Nathalie (2014) Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort.; Breast cancer research and treatment; vol. 145 (no. 2); 535-43

Appendices

Appendix A Review protocols

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

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362316
1.	Review title	Effects of hormone replacement therapy for menopausal symptoms on developing Breast cancer
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?
3.	Objective	To update the recommendations in NG23
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • INAHTA • HTA via CRD • PsycInfo Searches will be restricted by: • Date (2015 to date) • English language only • Human studies only

ID	Field	Content
		• RCTs, Systematic Reviews and Cohort 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 menopause (including perimenopause and postmenopause)

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

8.	Comparator/Reference standard/Confounding factors	• 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 • People with early menopause (aged 40 to 44)

ID	Field	Content
		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 adjust for confounders. Relevant confounders may include BMI, age at menopause, family history of breast cancer
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• Incidence of invasive breast cancer • Mortality from breast cancer
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the 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

ID	Field	Content
		• 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 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: • All-cause 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:

ID	Field	Content	
		• Recency of HRT use (current users, < 5 years, 5-9 years, ≥ 10 years since last use) by duration of HRT use (<1 year, 1-4 years, 5-9 years, 10-14 years, ≥ 15 years) Additional stratification will be done only for a single specified duration and recency of HRT use (for example: only current HRT users with 5 to 14 years of use) and will only be possible if evidence is reported in this way. Evidence will be stratified by: • Age at first use (45-50 years, 50-59 years, 60-69 years, >69 years) • Time since menopause at first use (<1 year, 1-4 years, 5-9 years, >10 years) • Constituent (equine oestrogen, oestradiol) • Mode of administration (oral, transdermal) • Progestogenic constituent (for combined HRT only: (Levo)norgestrel, Norethisterone acetate, Medroxyprogesterone acetate, Micronised progesterone, any synthetic progestin) • Length of cycle (for sequential combined HRT only: Sequential long cycle [3 monthly], Sequential 30 day cycle) • Family history of breast cancer (family history, no family history) • Personal history of breast cancer (personal history, no personal history) • For high risk of familial breast cancer (BRCA1/2 positive, BRCA1/2 negative) • 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) ○ 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

ID	Field	Content		
		☐	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	☒	☒
		Risk of bias (quality) assessment	☒	☒
		Data analysis	☒	☒
24.	Named contact	**5a. Named contact** Guideline development team NGA **5b Named contact e-mail** menopause@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Senior Systematic Reviewer • Systematic Reviewer		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		

ID	Field	Content	
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:	
29.	Other registration details	None	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362316	
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		
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

ID	Field	Content
35.	Additional information	
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; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HRT: Hormone Replacement Therapy; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS: risk of bias in non-randomised studies of interventions; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B Literature search strategies

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

One combined search was conducted for the following review questions:

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

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

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

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

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

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

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

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

Clinical searches

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

Date of last search: 03/10/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	56226
3	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
4	("change of life" or life change?).ti,ab.	3175
5	or/1-4	117224
6	exp Hormone Replacement Therapy/	26181
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Estrogens/	97369

#	Searches	
10	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or oestrogen* 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 oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or oestrogen* 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

1

2 Database: Embase <1974 to 2022 September 30>

3 Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
9	exp *oestrogen/	126164

#	Searches	
10	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
11	(oestrogen* or oestrogen* 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

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

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

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

3 Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938
4	or/1-3	15066
5	hormone therapy/	2262
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942

#	Searches	
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *estrogens/	5657
9	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
10	(oestrogen* or oestrogen* 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

#	Searches	
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *estrogens/	5657
73	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or oestrogen* 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

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

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

3 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 oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or oestrogen* 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

#	Searches	
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

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 oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or oestrogen* 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 oestrogen* OR oestradiol* OR estradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR ((combin* OR sequen* OR continu* OR plus) AND (progest* OR gestagen* OR gestogen* OR medroxyprogesterone* OR norgestrel* OR drospirenone* OR norethisterone* OR dydrogesterone* OR levonorgestrel*)) OR (("body identical*" OR bio-identical* OR bioidentical*) AND hormon*))	
3	1 AND 2	7537

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES	191
9	((hormon* AND (replac* or therap* or substitut*)))	1577
10	((HRT or HT or MHT or ERT or EPRT or SEPRT))	435
11	MeSH DESCRIPTOR Estrogens EXPLODE ALL TREES	136
12	((oestrogen* or oestrogen* 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 oestrogen* 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

#	Searches	
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352
55	26 and 54	849

1

1 Database: Embase <1974 to 2022 July 27>

2 Date of last search: 28/07/2022

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

#	Searches	
52	38 or 51	1266430
53	24 and 52	2248

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

Date of last search: 01/08/2022

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

1

2 Database: EconLit <1886 to July 21, 2022>

3 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

4

Database: CRD HTA

Date of last search: 28/07/2022

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

Database: INAHTA

Date of last search: 28/07/2022

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

Database: EED

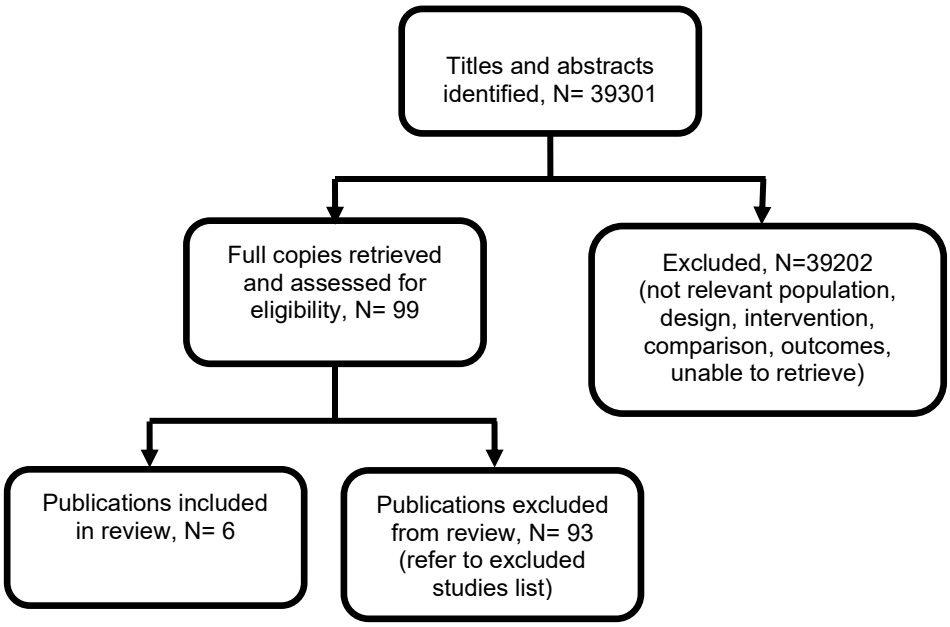
Date of last search: 28/07/2022

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

Appendix C Effectiveness evidence study selection

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

Figure 1: Study selection flow chart



Appendix D Evidence tables

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

Beral 2019

Beral, Valerie et al. (2019) Menopausal hormone therapy and 20-year breast cancer mortality. The Lancet 394 (10204): 1139

(Additional publication used for trial information and critical appraisal: *Green J, Reeves GK, Floud S, Barnes I, Cairns BJ, Gathani T, Pirie K, Sweetland S, Yang TO, Beral V; Million Women Study Collaborators. Cohort Profile: the Million Women Study. (2019) Int J Epidemiol 48(1):28-29e.* Beral 2019 used to extract outcome information)

Country/ies where study was carried out	United Kingdom
Study type	Prospective cohort study
Study dates	1996 to 2018
Inclusion criteria	• Born in 1935-1950 (eligible age range 50-64 at recruitment) • Postmenopausal • Free from breast cancer at recruitment
Exclusion criteria	None reported
Patient characteristics	**Age at recruitment, years – mean (SD)** 56 (5) (per arm not reported) **BMI kg/m2 – mean (SD)** 26 (5) (per arm not reported) **Ethnicity** White – 96% (per arm not reported) **Current use of menopausal hormone therapy** 33% (per arm not reported)

Intervention(s)/control	**Intervention:** Oestrogen-only menopausal hormone therapy Oestrogen plus progestogen hormone therapy **Control:** No hormone therapy
Sources of funding	Not industry funded
Sample size	N=907162
Other information	Published correspondence for data from the Million Women Study (*Green J, Reeves GK, Floud S, Barnes I, Cairns BJ, Gathani T, Pirie K, Sweetland S, Yang TO, Beral V; Million Women Study Collaborators. Cohort Profile: the Million Women Study. (2019) Int J Epidemiol 48(1):28-29e)*

Outcomes

Oestrogen and progestogen

Outcome – mortality from breast cancer	**HRT users vs Non-HRT users**
Current user <5 years use Rate ratio/95% CI	1.39 (1.27 to 1.53)
Current user 5+ years use Rate ratio/95% CI	1.64 (1.52 to 1.76)

Oestrogen-only

Outcome – mortality from breast cancer	**HRT users vs Non-HRT users**
Current user <5 years use Rate ratio/95% CI	1.15 (1.01 to 1.32)
Current user 5+ years use Rate ratio/95% CI	1.35 (1.24 to 1.47)

1 **Critical appraisal**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Not enough information to assess bias)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of the follow up and start of intervention coincided)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined and the definition is based on the information collected at the time of the intervention (information from electronic linkage databases))*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Serious *(Not enough information to assess bias)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was reasonably complete)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Serious *(Not enough information to assess bias)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Serious *(Not enough information to assess bias)*
Overall bias	Risk of bias judgement	Serious *(Not enough information for most domains to assess bias)*
Overall bias	Directness	Directly applicable

2

1 # Brusselaers, 2018

Bibliographic Reference	Brusselaers, N; Tamimi, R M; Konings, P; Rosner, B; Adami, H-O; Lagergren, J; Different menopausal hormone regimens and risk of breast cancer.; Annals of oncology : official journal of the European Society for Medical Oncology; 2018; vol. 29 (no. 8); 1771-1776

2 **Study details**

Country/ies where study was carried out	Sweden
Study type	Retrospective cohort study
Study dates	1 July 2005 to 31 December 2012
Inclusion criteria	• At least 1 hormone therapy prescription dispensed between 1 July 2005 and 31 December 2012 • 40 years or older
Exclusion criteria	• Younger than 40 years • history of malignancy (expect nonmelanoma skin cancer) identified from the Swedish Cancer Registry at the time of the first prescription
Patient characteristics	**Age-group, n (%)** <60 Ever menopausal hormone therapy users: 108631 (37.4) Never menopausal hormone therapy users: 325747 (37.4) 60-69 Ever menopausal hormone therapy users: 93490 (32.2) Never menopausal hormone therapy users: 267323 (30.8) ≥70 Ever menopausal hormone therapy users: 88065 (30.4) Never menopausal hormone therapy users: 277095 (31.8) Mean age, years (SD): not reported
Intervention(s)/control	**Intervention:** User of menopausal hormone therapy - defined as at least one prescription dispensed.

	Information on prescription available from the Swedish Prescribed Drug Registry, that has individual-level data on drug prescriptions in Sweden with over 99% completeness. Over the counter prescriptions and hospital prescriptions are not included. If women were prescribed progestogen HT during the study period they were considered oestrogen + progestogen users. **Comparison:** Non-users of menopausal hormone therapy - defined as no hormone therapy prescription during the study period
Sources of funding	Not industry funded - Swedish Research Council; Swedish Cancer Society, Epidemiology Karolinska Institutet
Sample size	N=1160351 Ever menopausal hormone therapy users: n=290186 Never menopausal hormone therapy users: n=870165
Other information	Adjusted for confounders: • hysterectomy • ever parous • thrombotic events • year of birth • smoking-related diseases • alcohol-related diseases • obesity • diabetes mellitus • osteoporosis Current HRT users – oestrogen-only: <12 months, n=3047 12-35 months, n=6343 >=36 months, n=7318

Outcomes

Oestrogen-only

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Current HRT users (at least 1 prescription in last 6 months of follow-up) - age at first prescription <60 adjusted OR Odds ratio/95% CI	0.63 (0.54 to 0.73)
Current HRT users - age at first prescription 60-69 Odds ratio/95% CI	1.65 (1.51 to 1.81)
Current HRT users - age at first prescription 70 or over Odds ratio/95% CI	1.17 (1.08 to 1.27)
Current HRT users – all ages Odds ratio/95% CI	1.08 (1.02 to 1.14)
Past HRT users - age at first prescription <60 Odds ratio/95% CI	0.54 (0.46 to 0.62)
Past HRT users - age at first prescription 60-69 Odds ratio/95% CI	0.73 (0.66 to 0.81)
Past HRT users - age at first prescription 70 or over Odds ratio/95% CI	0.58 (0.53 to 0.64)
Past HRT users – all ages Odds ratio/95% CI	0.63 (0.60 to 0.67)

1 **Oestrogen-only, 1-4 current years of use, mode of administration**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Oral Odds ratio/95% CI	1.08 (1.02 to 1.15)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Cutaneous (Transdermal) Odds ratio/95% CI	1.19 (1.05 to 1.36)

1 **Oestrogen-only, by constituent, for 1-4 years current use**

Outcome	HRT users vs Non-HRT users
Estradiol Odds ratio/95% CI	1.12 (1.04 to 1.20)
Estriol Odds ratio/95% CI	0.76 (0.69 to 0.84)
Conjugated oestrogens Odds ratio/95% CI	4.47 (2.67 to 7.48)

2 **Oestrogen + Progestogen**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Current HRT user - age at first prescription <60 Odds ratio/95% CI	0.79 (0.73 to 0.87)
Current HRT user - age at first prescription 60-69 Odds ratio/95% CI	2.38 (2.22 to 2.55)
Current HRT users - age at first prescription 70 or over Odds ratio/95% CI	3.59 (3.3 to 3.91)
Current HRT users – all ages **Odds ratio/95% CI**	1.77 (1.69 to 1.85)
Past HRT user - age at first prescription <60	0.5 (0.45 to 0.56)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Odds ratio/95% CI	
Past HRT user - age at first prescription 60-69 Odds ratio/95% CI	0.9 (0.83 to 0.97)
Past HRT user - age at first prescription 70 or over Odds ratio/95% CI	1.18 (1.07 to 1.29)
Past HRT users – all ages **Odds ratio/95% CI**	0.89 (0.84 to 0.93)

1 **Oestrogen + Progestogen, 1-4 current years of use, mode of administration**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Oral Odds ratio/95% CI	1.86 (1.77 to 1.95)
Cutaneous (Transdermal) Odds ratio/95% CI	1.40 (1.20 to 1.64)

2 **Oestrogen and progestogen, by frequency of progestogen, current users 1-4 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Continuous Odds ratio/95% CI	2.18 (1.99 to 2.40)
Sequential Relative risk/95% CI	1.37 (0.97 to 1.92)

3 **Critical appraisal**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Not all confounders adjusted for: age at menopause; family history of breast cancer)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of the follow up and start of intervention coincided)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined and the definition is based on the information collected at the time of the intervention (information from Swedish Prescribed Drug Register))*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on possible co-interventions that may affect breast cancer incidence. The intervention is assumed to have been implemented successfully, however it is based on the assumption that dispensed prescription means use of the hormone therapy, and that is unknown.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was reasonably complete)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Method of outcome assessment likely to be comparable across intervention groups and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes, and are available to view on the clinical database. Multiple adjusted analyses reported)*
Overall bias	Risk of bias judgement	Moderate *(Most domains are low risk of bias, however, potential for bias due to confounding as not all potential confounders were adjusted for)*
Overall bias	Directness	Directly applicable

1 Chen, 2002

Bibliographic Reference	Chen, Chi-Ling; Weiss, Noel S; Newcomb, Polly; Barlow, William; White, Emily; Hormone replacement therapy in relation to breast cancer.; JAMA; 2002; vol. 287 (no. 6); 734-41

2 Study details

Country/ies where study was carried out	United States
Study type	Retrospective cohort study
Study dates	1 July 1990 to 31 December 1995
Inclusion criteria	Cases: • Enrolled in the Group Health Cooperative of Puget Sound continuously for at least 2 years before diagnosis of cancer date. • Women aged 50 to 74 years who have been newly diagnosed as having a primary invasive breast cancer between 1 July 1990 and 31 December 1995. • Identified through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry. Controls: • Enrolled in the Group Health Cooperative of Puget Sound during the years the cases were diagnosed.
Exclusion criteria	• Hormone replacement therapy by patch or injection, or progestin cream.
Patient characteristics	**Age at reference date (1 year before breast cancer diagnosis), number (%)** <50 Cases: 17 (2.4) Controls: 15 (2.2) 50-54 Cases: 113 (16) Controls: 116 (16.8) 55-59 Cases: 145 (20.6) Controls: 131 (18.9)

	60-64 Cases: 149 (21.1) Controls: 150 (21.7) 65-70 Cases: 182 (25.8) Controls: 170 (24.6) ≥70 Cases: 99 (14.0) Controls: 110 (15.9) Mean age, years (SD): not reported **Age at menopause:** ≤44 Cases: 140 (19.9) Controls: 155 (22.4) 45-49 Cases: 244 (34.6) Controls: 221 (31.9) 50-54 Cases: 259 (36.7) Controls: 246 (35.6) ≥55 Cases: 46 (6.5) Controls: 45 (6.5) **Family history of breast cancer** None: Cases: 427 (65.2) Controls: 470 (74.8) Second-degree relatives only Cases: 93 (14.2) Controls: 70 (11.1) First degree relatives only Cases: 135 (20.6) Controls: 88 (14.0)

Intervention(s)/control	Intervention: • Had a prescription dispensed from the pharmacy for hormonal replacement therapy. • Prescribed oestrogen and progestin oral pills, or topical oestrogen vaginal cream. • Topical oestrogen vaginal cream not included in the analysis for this review as does not fit the protocol. • Past hormone replacement therapy use defined from pharmacy records for 5 and 10 years before reference date (date of breast cancer diagnosis, or matched date for control group). • Current use defined as having at least 2 prescriptions for hormone replacement therapy during the 6 month period before reference date. Comparison: • No record of hormone replacement therapy on pharmacy records.
Duration of follow-up	5 or 10 years follow-up period before the reference date
Sources of funding	Not industry funded - supported in part by Breast Cancer Surveillance Cooperative Agreement from the National Cancer Institute
Sample size	Only those with pharmacy records included in the analysis for this review. 5 year use: N=1104 Cases: n=553 Controls: n=551 10 year use: N= 855 Cases: n=428 Controls: n=427
Other information	Potential confounders identified were: age at reference, age at menarche, age at menopause, type of menopause, parity, age at first birth, family history of breast cancer, years of oral contraceptive use, measures of screening mammography before diagnosis, Only those factors that changed the odds ratio estimates were included in the co-variate-adjusted models. Age at reference, year of breast cancer diagnosis, number of mammograms before diagnosis were found to be confounders and were adjusted for in the final models. Outcome table includes estimates from the study where the months of HRT use do not overlap.

	Not enough information on the time since last use, as past users are defined as no use in the most recent 6 months since diagnosis of cancer (or matched date for the matched group).

1 **Outcomes**

2 **Oestrogen-only**

Outcome – Incidence of breast cancer	**HRT users vs non-HRT users**
Past use, >6 months since last use, duration of use 1-4 years between 37-59 months Odds ratio/95% CI	1.45 (0.84 to 2.49)
Past use, >6 months since last use, duration of use 5 years Odds ratio/95% CI	1.84 (1.04 to 3.27)

3 **Any combined oestrogen and progestogen**

Outcome – Incidence of breast cancer	**HRT users vs non-HRT users**
Past use, >6 months since last user, duration of use 12 months or less Odds ratio/95% CI	1.25 (0.79 to 1.98)
Past use, >6 months since last use, duration of use 1-4 years Odds ratio/95% CI	1.20 (0.75 to 1.93)

4 **Continuous combined oestrogen and progestogen**

Outcome – Incidence of breast cancer	**HRT users vs non-HRT users**
Current use, duration of use 6 months or less Odds ratio/95% CI	0.85 (0.36 to 2.03)
Past use, >6 months since last use, duration of use 1-4 years Odds ratio/95% CI	1.85 (0.81 to 4.21)

5 **Sequential combined oestrogen and progestogen**

Outcome – Incidence of breast cancer	HRT users vs non-HRT users
Past use, >6 months since last use, duration of use 1-4 years Odds ratio/95% CI	1 (0.59 to 1.71)

1 **Critical appraisal**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(Important confounders were adjusted for)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of follow up and start of intervention coincided)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined and the definition is based on the information collected at the time of the intervention (pharmacy database).)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on possible co-interventions that may affect breast cancer incidence. The intervention is assumed to have been implemented successfully, however it is based on the assumption that a dispensed prescription for hormone treatment would mean the use of the therapy - it is not possible to know this.))*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was reasonably complete)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Method of outcome assessment was likely comparable across intervention groups and the outcome measure was unlikely to be*

Section	Question	Answer
		influenced by knowledge of the intervention received by study participants)
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes, and are available to view on the clinical database. Multiple adjusted analyses reported)*
Overall bias	Risk of bias judgement	Low *(Most domains rated as low risk of bias)*
Overall bias	Directness	Directly applicable

1 ## Chlebowski, 2020

Bibliographic Reference Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, Barrington W, Kuller LH, Simon MS, Lane D, Johnson KC, Rohan TE, Gass MLS, Cauley JA, Paskett ED, Sattari M, Prentice RL (2020) Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality during Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 324(4): 369-380

2 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Study dates	Conjugated equine oestrogen (CEE): Enrolment from 1993 to 1998, ended 2004. CEE plus progestin (medroxyprogesterone acetate MPA): Enrolment from 1993 to 1998, ended 2002.
Inclusion criteria	• Postmenopausal • aged 50-74 • provided written informed consent • baseline mammogram not suggestive of cancer

	• consent for survival linkage at baseline. • Had undergone hysterectomy (for the oestrogen-only study).
Exclusion criteria	• Prior breast cancer • anticipated survival of less than 3 years.
Patient characteristics	**CEE-alone trial** Age at screening, mean (SD) - years: CEE: 63.6 (7.3) Placebo: 63.6 (7.3) Race - White, n (%): CEE: 4009 (75.5) Placebo: 4075 (75.1) Race - Black, n (%): CEE: 781 (14.7) Placebo: 835 (15.4) Race - Hispanic/American Indian/ Asian, Pacific Islander/ Unknown: CEE: 520 (9.8) Placebo: 519 (9.5) First-degree female relatives with breast cancer: CEE: 696 (14.2) Placebo: 685 (13.6) **CEE+MPA trial** Age at screening, mean (SD) - years: CEE+MPA: 63.2 (7.1) Placebo: 63.3 (7.1) Race - White, n (%): CEE+MPA: 7141 (84) Placebo: 6805 (84) Race - Black, n (%): CEE+MPA : 548 (6.4) Placebo: 574 (7.1)

	Race - Hispanic/American Indian/ Asian, Pacific Islander/ Unknown: CEE+MPA: 817 (9.6) Placebo: 723 (8.9) First-degree female relatives with breast cancer: CEE+MPA: 1009 (12.7) Placebo: 895 (11.8)
Intervention(s)/control	**CEE only trial:** Intervention: Women received 0.625 mg/d of conjugated oestrogen-only Placebo: Women received matching placebo **CEE+MPA trial:** Intervention: Women received 1 daily tablet containing conjugated equine oestrogen 0.625 mg, and medroxyprogesterone acetate 2.5mg Placebo: Women received a matching placebo
Duration of follow-up	Median 20.7 years (IQR. 19.7 to 21.7)
Sources of funding	Not industry funded
Sample size	**CEE only trial:** N=10739 CEE: n=5310 Placebo: n=5429 **CEE+MPA trial:** N=16608 CEE+MPA: n=8506 Placebo: n=8102
Other information	Data from the Women's Health Initiative randomised controlled trial. The studies were stopped early after a median intervention period of 7.2 years in the CEE only, and 5.6 years in the CEE+MPA trials. However, follow-up on mortality continued using data from the National Death Index.

Outcomes

CEE only

Outcome	CEE, N = 5310	Placebo (CEE trial), N = 5429	HR (95% CI)
Death from breast cancer No of events	n = 30	n = 46	0.60 (0.37 to 0.97)
Breast cancer incidence - non-Hispanic White ethnicity	n = 189	n = 232	0.80 (0.66 to 0.97)
Breast cancer incidence - Non-Hispanic Black ethnicity	n = 24	n = 49	0.52 (0.31 to 0.88)
Breast cancer incidence - First-degree relative with breast cancer	n = 54	n = 45	1.28 (0.77 to 2.11)
Breast cancer incidence - No first-degree relative with breast cancer	n = 168	n = 228	0.72 (0.59 to 0.89)

CEE+MPA

Outcome	CEE+MPA, N = 8506	Placebo (CEE+MPA trial), N = 8102	HR (95% CI)
Death from breast cancer	n = 71	n = 53	1.35 (0.94 to 1.95)
Breast cancer incidence - non-Hispanic White ethnicity	n = 511	n = 392	1.24 (1.08 to 1.42)

Outcome	CEE+MPA, N = 8506	Placebo (CEE+MPA trial), N = 8102	HR (95% CI)
Breast cancer incidence - Non-Hispanic Black ethnicity	n = 35	n = 28	1.35 (0.79 to 2.30)
Breast cancer incidence - First-degree relative with breast cancer	n = 94	n = 62	1.44 (1.01 to 2.05)
Breast cancer incidence - No first-degree relative with breast cancer	n = 457	n = 359	1.25 (1.09 to 1.45)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation sequence was random and concealed until enrolment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were blinded)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Assessed under 2a)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Mortality data available for 98% of participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Mortality data came from the National Data Index so measurement could not have differed between groups.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Mortality data collected as specified)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall directness	Directly applicable

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 oophorectomy) 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) RCTs (average across 6 RCTs): **Age at entry, years – mean:** 63.5 (SD not reported)
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)	Not industry funded
Sample size	Prospective studies:

	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-only - current users

Outcome – Incidence of breast cancer	**HRT users vs Non-HRT users**
Current use, Duration <1 year use Relative risk/95% CI	1.08 (0.86 to 1.35)
Current use, duration 1-4 years Relative risk/95% CI	1.17 (1.1 to 1.26)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Current use, duration 5-9 years Relative risk/95% CI	1.22 (1.17 to 1.28)
Current use, duration 10-14 years Relative risk/95% CI	1.43 (1.37 to 1.5)
Current use, duration of use 15 or more years Relative risk/95% CI	1.58 (1.51 to 1.66)

1 **Oestrogen-only, past users**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users, 1-4 years,	HRT users vs Non-HRT users, 5-9 years	HRT users vs Non-HRT users, 10+ years
Duration <1 year use Relative risk/95% CI	1.12 (0.93 to 1.36)	1.06 (0.88 to 1.28)	0.99 (0.87 to 1.12)
Duration 1-4 years use Relative risk/95% CI	1.03 (0.92 to 1.15)	1.07 (0.96 to 1.2)	1.04 (0.95 to 1.13)
Duration 5-9 years use Relative risk/95% CI	1.06 (0.97 to 1.16)	1.06 (0.97 to 1.16)	1.14 (1.04 to 1.25)
Duration over 10 years use Relative risk/95% CI	1.21 (1.13 to 1.3)	1.2 (1.12 to 1.3)	1.29 (1.16 to 1.42)

2 **Oestrogen-only, age at first use, during 5-14 years of current use**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
40-44 years Relative risk/95% CI	1.33 (1.19 to 1.48)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
45-49 years Relative risk/95% CI	1.39 (1.3 to 1.48)
50-54 years Relative risk/95% CI	1.33 (1.25 to 1.42)
55-59 years Relative risk/95% CI	1.26 (1.12 to 1.41)
60-69 years Relative risk/95% CI	1.08 (0.9 to 1.31)

1 **Oestrogen-only, by constituent, for 5-14 years current use**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Equine oestrogen Relative risk/95% CI	1.32 (1.25 to 1.39)
Estradiol Relative risk/95% CI	1.38 (1.3 to 1.46)
Estropipate Relative risk/95% CI	1.09 (0.79 to 1.51)
Oestriol Relative risk/95% CI	1.24 (0.89 to 1.73)

2 **Oestrogen-only, 5-14 current years of use, mode of administration**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Oral	1.33 (1.27 to 1.38)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Relative risk/95% CI	
Transdermal Relative risk/95% CI	1.35 (1.25 to 1.46)

1 **Oestrogen-only, time since menopause and first MHT use, current uses 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
<5 years after menopause Relative risk/95% CI	1.37 (1.29 to 1.45)
5+ years after menopause Relative risk/95% CI	1.21 (1.06 to 1.38)

2 **Oestrogen-only, factors identified in the equalities section of the scope, current use 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
White ethnicity Relative risk/95% CI	1.32 (1.28 to 1.37)
Other ethnicity Relative risk/95% CI	1.39 (1.16 to 1.66)
Education <13 years (proxy for deprived socioeconomic group) Relative risk/95% CI	1.28 (1.21 to 1.35)
Education 13 or more years (proxy for deprived socioeconomic group) Relative risk/95% CI	1.35 (1.28 to 1.43)

3 **Oestrogen-only, family history of breast cancer, current use 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Family history Relative risk/95% CI	1.35 (1.21 to 1.50)
No family history Relative risk/95% CI	1.31 (1.25 to 1.37)

1 **Oestrogen and progestogen - current users**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Duration <1 years use Relative risk/95% CI	1.2 (1.01 to 1.43)
Duration 1-4 years use Relative risk/95% CI	1.6 (1.52 to 1.69)
Duration 5-9 years use Relative risk/95% CI	1.97 (1.9 to 2.04)
Duration 10-14 years use Relative risk/95% CI	2.26 (2.16 to 2.36)
Duration 15 or more years use Relative risk/95% CI	2.51 (2.35 to 2.68)

2 **Oestrogen and progestogen, past users**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users, 1-4 years	HRT users vs Non-HRT users, 5-9 years	HRT users vs Non-HRT users, 10+ years
<1 year duration of use Relative risk/95% CI	0.98 (0.85 to 1.14)	1 (0.89 to 1.14)	1.06 (0.95 to 1.19)

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users, 1-4 years	HRT users vs Non-HRT users, 5-9 years	HRT users vs Non-HRT users, 10+ years
1-4 years duration of use Relative risk/95% CI	1.18 (1.09 to 1.29)	1.06 (0.98 to 1.15)	1.09 (1 to 1.18)
5-9 years duration of use Relative risk/95% CI	1.21 (1.14 to 1.29)	1.23 (1.15 to 1.3)	1.19 (1.1 to 1.28)
10 or more years of use Relative risk/95% CI	1.34 (1.25 to 1.44)	1.28 (1.19 to 1.38)	1.28 (1.15 to 1.43)

1 **Oestrogen and progestogen, age at first use, during 5-14 years of current use**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
40-44 years Relative risk/95% CI	2.22 (1.96 to 2.52)
45-49 years Relative risk/95% CI	2.14 (2.03 to 2.26)
50-54 years Relative risk/95% CI	2.1 (2.01 to 2.21)
55-59 years Relative risk/95% CI	1.97 (1.81 to 2.15)
60-69 years Relative risk/95% CI	1.75 (1.48 to 2.06)

2 **Oestrogen and progestogen preparations, progestogenic constituent, current users 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Levonorgestrel Relative risk/95% CI	2.12 (1.99 to 2.25)
Norethisterone acetate Relative risk/95% CI	2.2 (2.09 to 2.32)
Medroxyprogesterone acetate Relative risk/95% CI	2.07 (1.96 to 2.19)
Micronised progesterone Relative risk/95% CI	2.05 (1.38 to 3.06)
Dydrogesterone (synthetic progestogen/progestin) Relative risk/95% CI	1.41 (1.17 to 1.71)
Promegestone (synthetic progestogen/progestin) Relative risk/95% CI	2.06 (1.19 to 3.56)
Nomegestrol acetate (synthetic progestogen/progestin) Relative risk/95% CI	1.38 (0.75 to 2.53)

1 **Oestrogen and progestogen, time since menopause and first MHT use, current users 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
< 5 years after menopause Relative risk/95% CI	2.12 (2.02 to 2.23)
5+ years after menopause Relative risk/95% CI	1.77 (1.6 to 1.95)

2 **Oestrogen-only, family history of breast cancer, current use 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Family history Relative risk/95% CI	2.11 (1.91 to 2.32)
No family history Relative risk/95% CI	2.02 (1.95 to 2.10)

1 **Oestrogen and progestogen, factors identified in the equalities section of the scope, current use 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
White ethnicity Relative risk/95% CI	2.08 (2.02 to 2.15)
Other ethnicity Relative risk/95% CI	2.13 (1.81 to 2.5)
Education <13 years (proxy for deprived socioeconomic group) Relative risk/95% CI	2.05 (1.96 to 2.15)
Education 13 or more years (proxy for deprived socioeconomic group) Relative risk/95% CI	2.03 (1.93 to 2.13)

2 **Oestrogen and progestogen, by frequency of progestogen, current users 5-14 years**

Outcome – Incidence of breast cancer	HRT users vs Non-HRT users
Daily (continuous) Relative risk/95% CI	2.3 (2.21 to 2.4)
Intermittent (sequential) usually 10-14 days progestogen per month Relative risk/95% CI	1.93 (1.84 to 2.01)

3 **Randomised controlled trials**

Outcome – Incidence of breast cancer	HRT users	Non-HRT users
Oestrogen-only No of events	n = 188, N=6530	n = 246, N=6635
Oestrogen and progestogen No of events	n = 491, N=12664	n = 373, N=12255

1 **Critical appraisal - CASP Critical appraisal checklist for IPD meta-analysis**

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*)
	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

Section	Question	Answer
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 included?	Yes (*details of methods provided in supplementary information*)
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

Section	Question	Answer
	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
	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

Section	Question	Answer
	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 ## Fournier, 2014

Bibliographic Reference Fournier, Agnes; Mesrine, Sylvie; Dossus, Laure; Boutron-Ruault, Marie-Christine; Clavel-Chapelon, Francoise; Chabbert-Buffet, Nathalie; Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort.; Breast cancer research and treatment; 2014; vol. 145 (no. 2); 535-43

2 **Study details**

Country/ies where study was carried out	France
Study type	Prospective cohort study
Study dates	Women enrolled in 1990, and completed questionnaires from 1992 to 2008

Inclusion criteria	• Post menopausal women, born between 1925 and 1950. • Insured by a national health insurance fund that mainly covers teachers and their family members. • Menopausal status and date of menopause were determined from regularly updated data on menstrual periods, hysterectomy, oophorectomy, MHT use, self reported menopausal status, and menopausal symptoms, as detailed elsewhere.
Exclusion criteria	• Premenopausal • no follow-up at all • diagnosed with cancer (other than a basal cell carcinoma) before follow-up started • who did not respond to the 1992 questionnaire about lifetime MHT use.
Patient characteristics	**Age at end of follow-up, years (mean ± SD)** Never user: 67.1 ± 7.8 Past user: 67.0 ± 5.8 Current user: 63.1 ± 5.5 **Age at menopause, years (mean ± SD)** Never user: 51.2 ± 3.9 Past user: 50.2 ± 3.7 Current user: 50.3 ± 3.6 **Body mass index (kg/m2), %** Never user: <18.5: 3.3% 18.5–22.9: 44.1% 23.0–24.9: 22.7% 25.0–29.9: 24.0% 30+: 6.0 % Past user: <18.5: 4.1 % 18.5–22.9: 38.7% 23.0–24.9: 21.0% 25.0–29.9: 26.2% 30+: 10.0% Current user: <18.5: 3.3%

	18.5–22.9: 50% 23.0–24.9: 22.5% 25.0–29.9: 20.1% 30+: 4%
Intervention(s)/control	Menopausal hormone therapy (MHT): current or past users of estrogenonly, or estrogen + progesterone/dydrogesterone.(Only information regarding estrogen + progesterone/dydrogesterone) has been extracted as there will be overlap with CGHFB 2019 regarding estrogen-only data). Control: never users of MHT
Duration of follow-up	16 years
Sources of funding	Not reported
Sample size	N = 79353 Never users: 21601 Past users: 31223 Current users: 17986
Other information	Cohort included in the Collaborative Group on Hormonal Factors in Breast (CGHFB) individual patient data meta-analysis, therefore only information on one subgroup has been extracted. There will be some overlap with the CGHFB group as some participants were included in their analysis, but there are more cases in this publication that are not in CGHFB.

1 **Outcomes**

2 **Oestrogen + progesterone/dydrogesterone, current users, 5+ years use**

Outcome – Incidence of breast cancer	**Current users vs No HRT use**
Breast cancer Hazard ratio/95% CI	1.31 (1.15 to 1.48)

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

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, age at menopause, year of birth, years of schooling, parity and age at first birth, BMI, type of menopause, age at menarche, pap smear frequency, history of breast cancer in relatives, personal history of benign breast disease, mammogram in previous follow-up period, use of oral contraceptives before menopause, use of progestogens before menopause.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	There is an increased risk of breast cancer with oestrogen + progesterone/dydrogesterone compared to no HRT use.
(B) What are the results?	8. How precise are the results?	The confidence intervals are slightly wide.
(B) What are the results?	9. Do you believe the results?	Yes, the study is large, has adjusted for multiple confounders.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes

Section	Question	Answer
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

BMI: body mass index; CASP: Critical Appraisal Skills Programme; CEE: conjugated equine oestrogen; CGHFB: Collaborative Group on Hormonal Factors in Breast; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; IQR: interquartile range; IPD: individual participant data; MHT: menopausal hormone therapy; MPA: medroxyprogesterone acetate; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomised controlled trial; SD: standard deviation

Appendix E Forest plots

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

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

Comparison 1: Any combined oestrogen and progestogen versus no HRT

Incidence of breast cancer

Figure 2: Current HRT users, by years of use

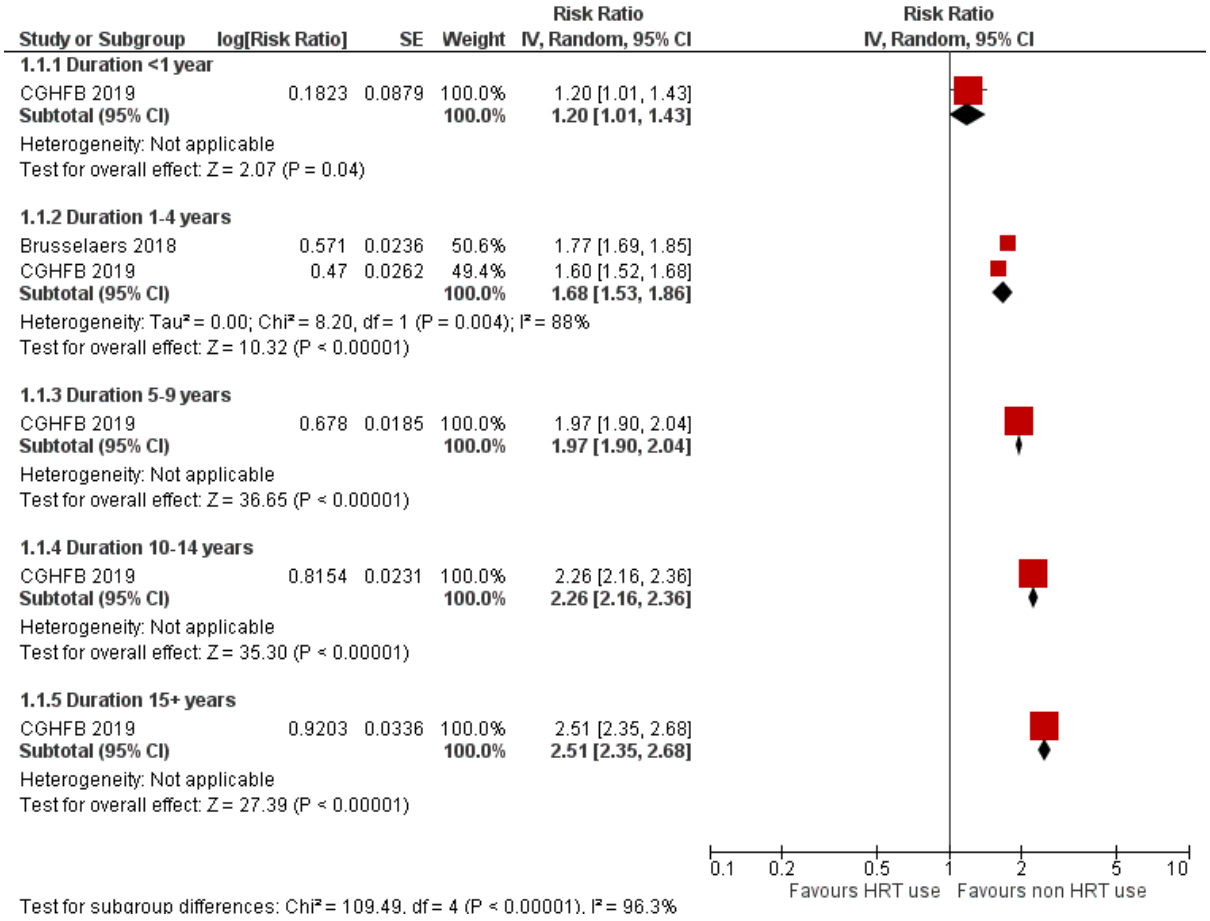


Figure 3: Past HRT users, <5 years since last use, by years of use

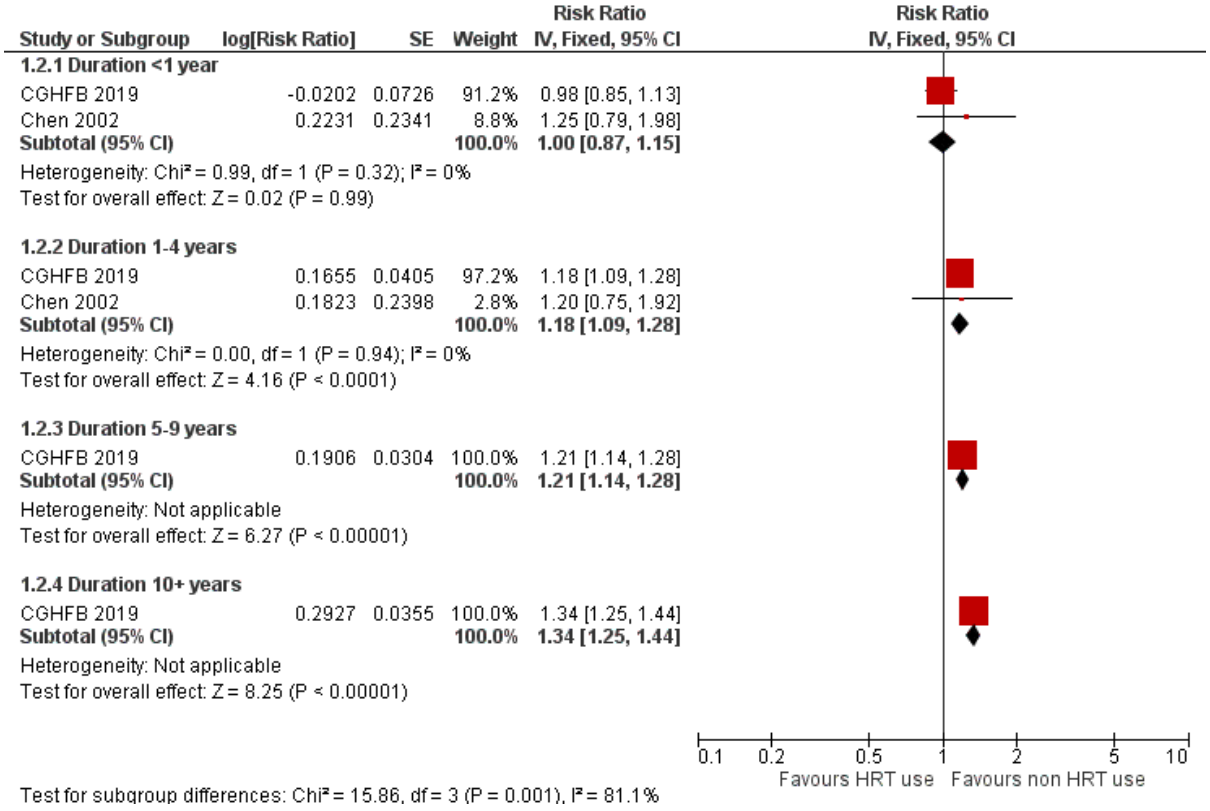


Figure 4: Past HRT users, 5-9 years since last use, by years of use

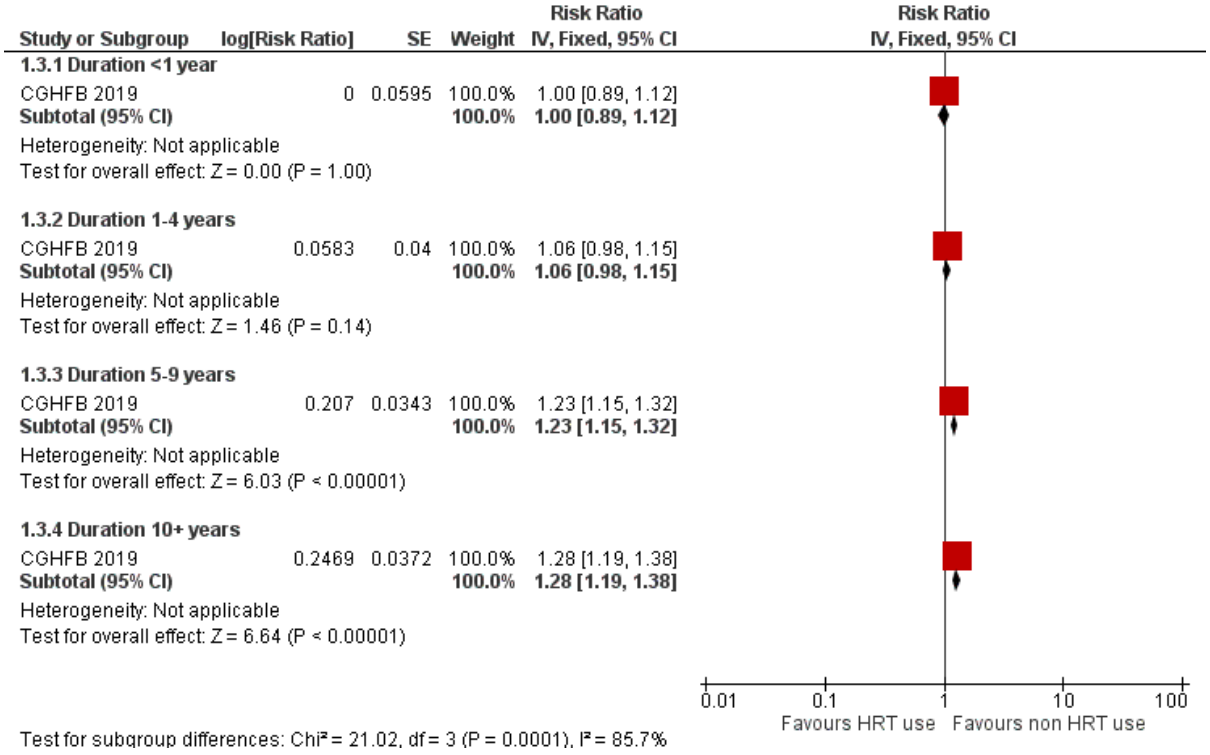


Figure 5: Past HRT users, 10+ years since last use, by years of use

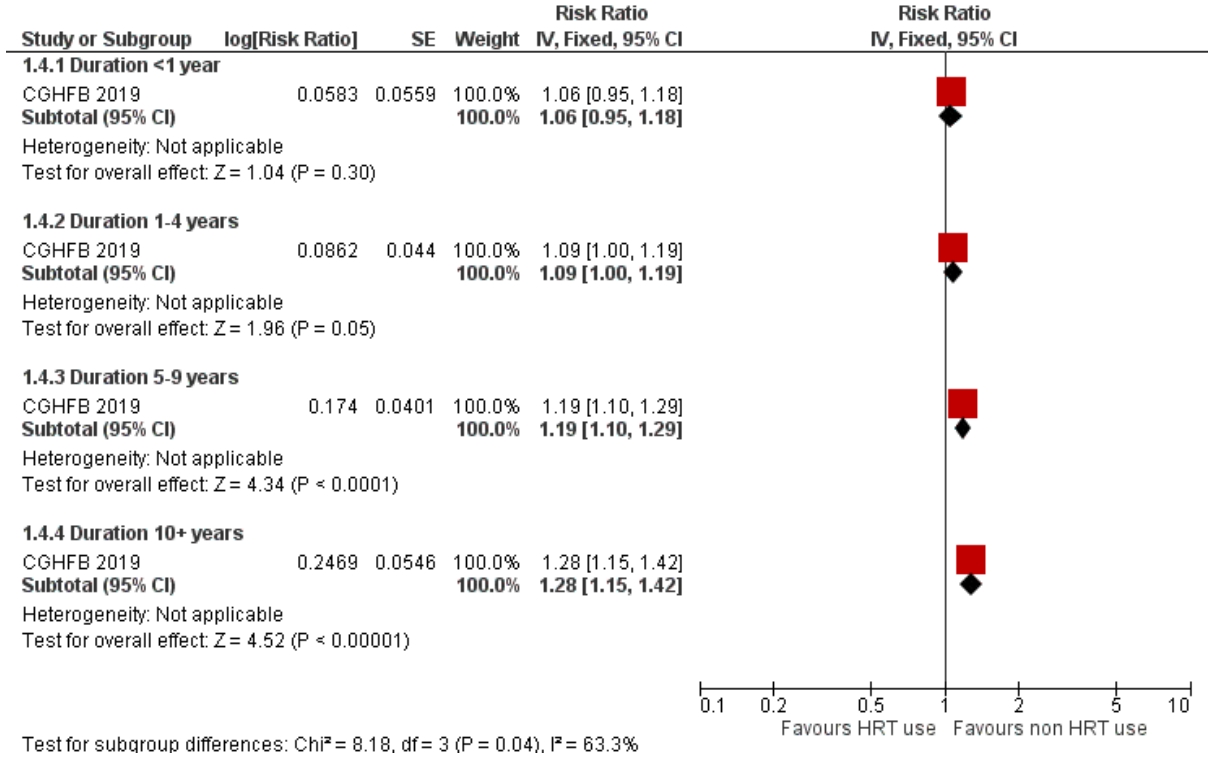


Figure 6: Age at first use, during 1-4 years current use

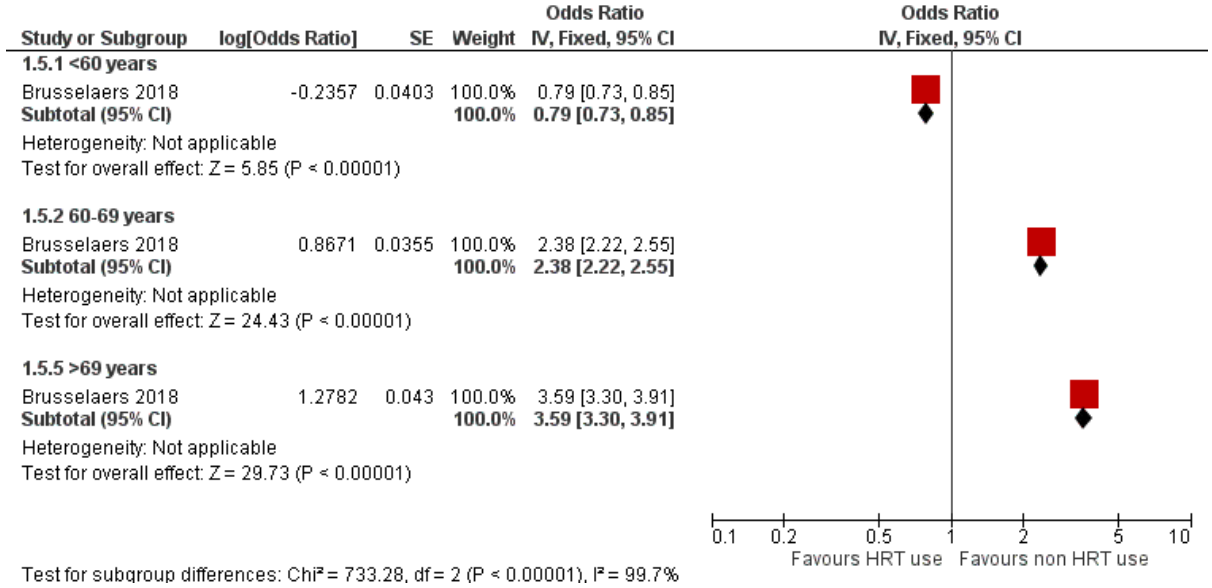


Figure 7: Age at first use, during 5-14 years current use

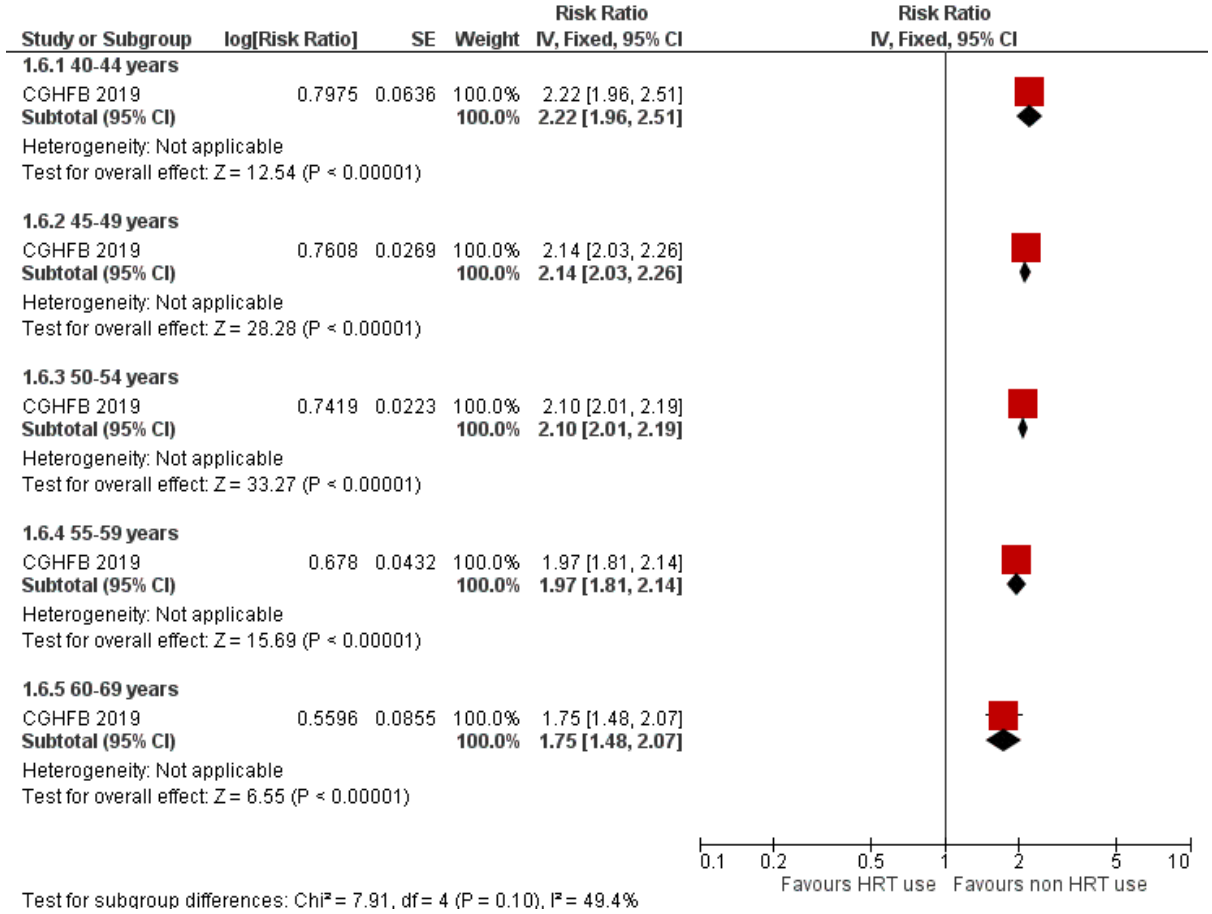


Figure 8: Progestogenic constituent, for 5-14 years current use

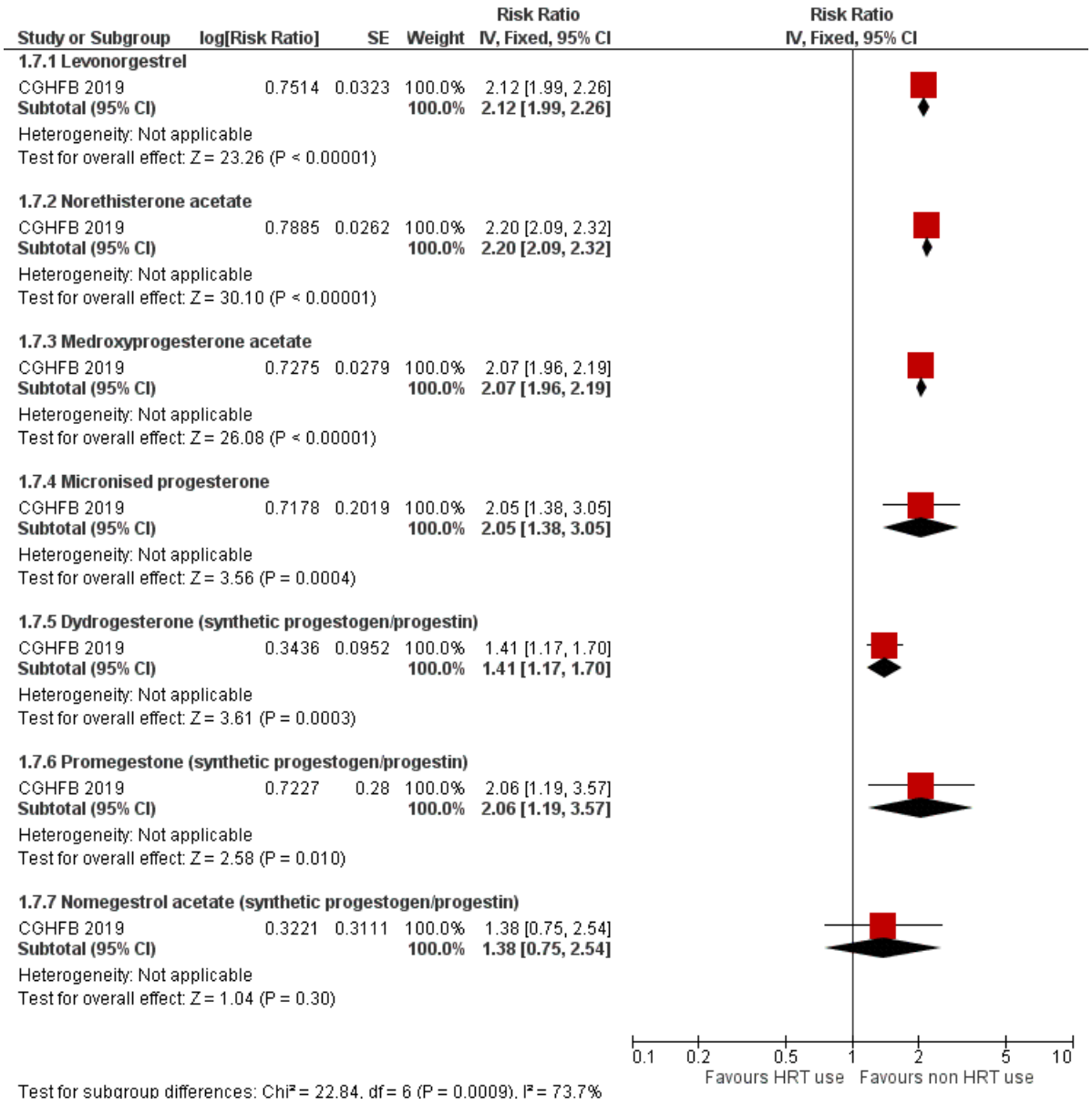


Figure 9: Family history of breast cancer, current use 5-14 years

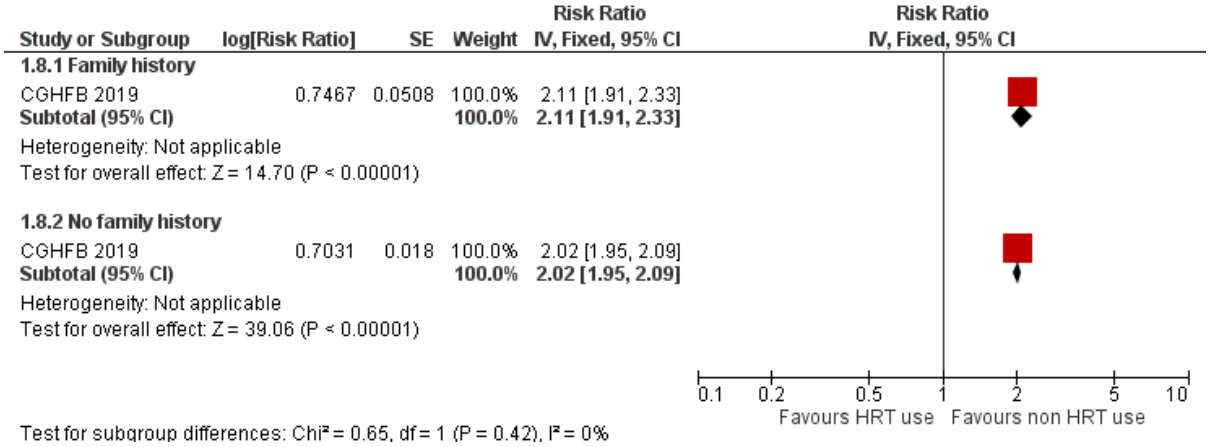


Figure 10: Education (proxy socioeconomic status), current use 5-14 years

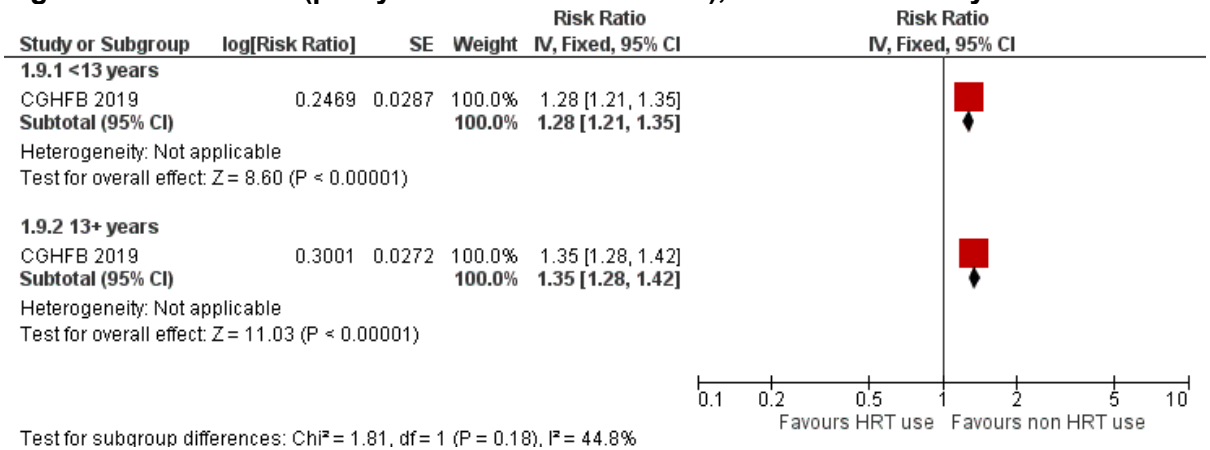


Figure 11: Time since menopause and first HRT use, for 5-14 years current use

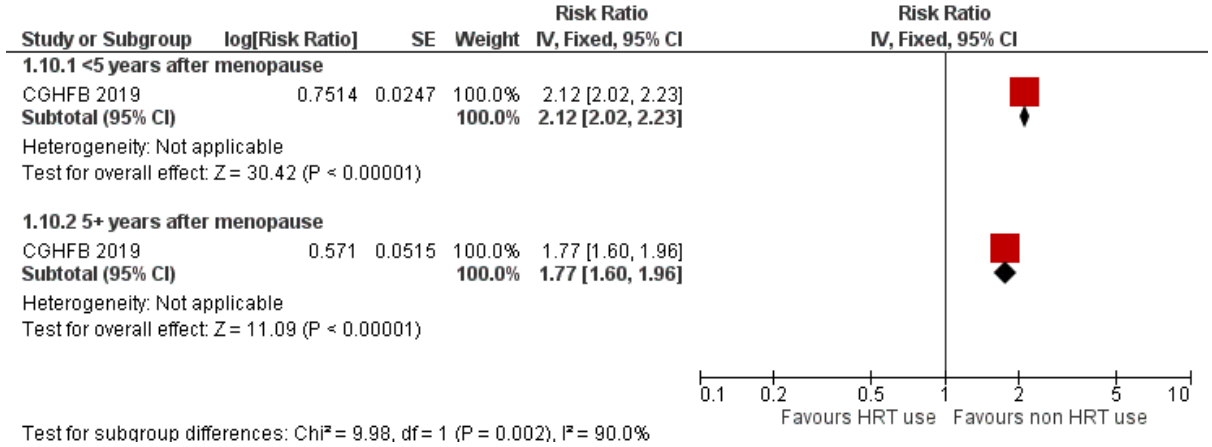


Figure 12: Ethnicity, current use 5-14 years

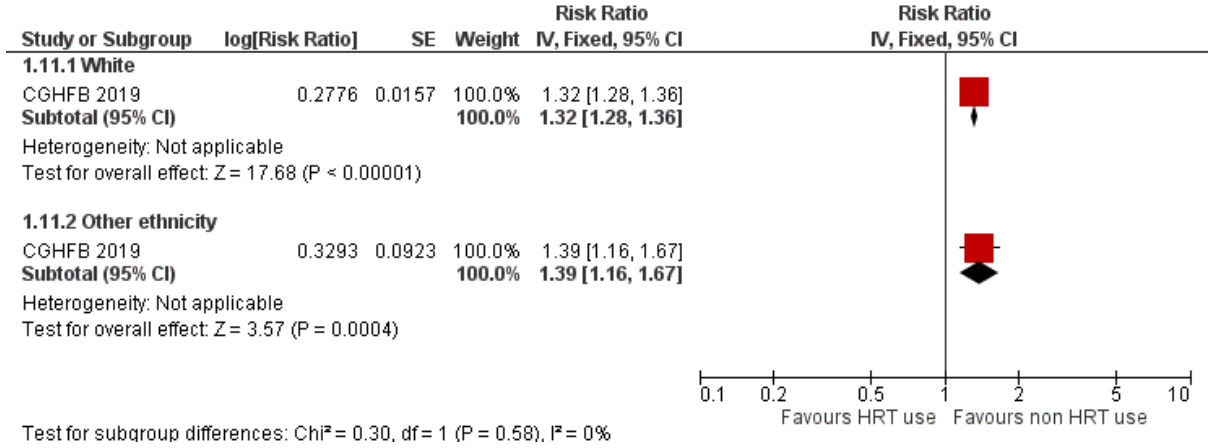


Figure 13: Mode of administration, for 1-4 years current use

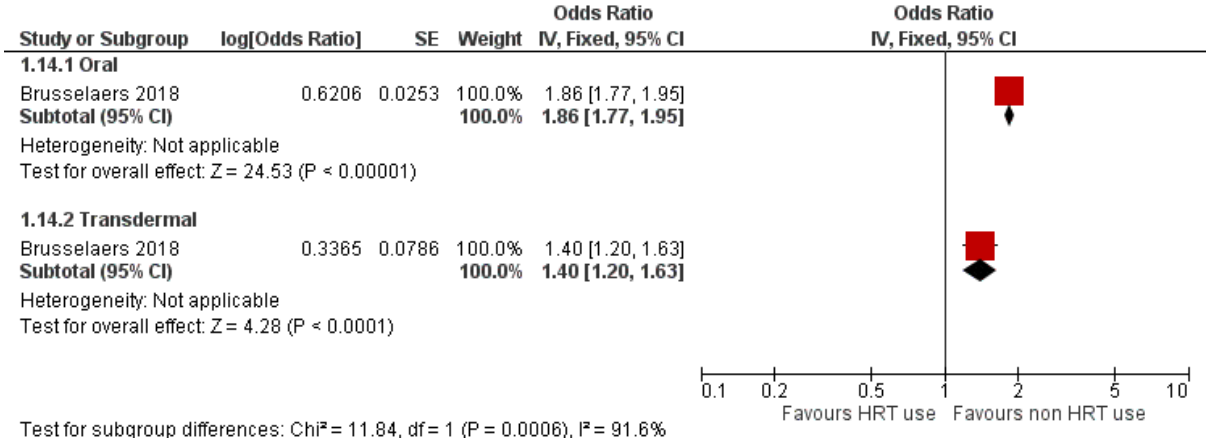
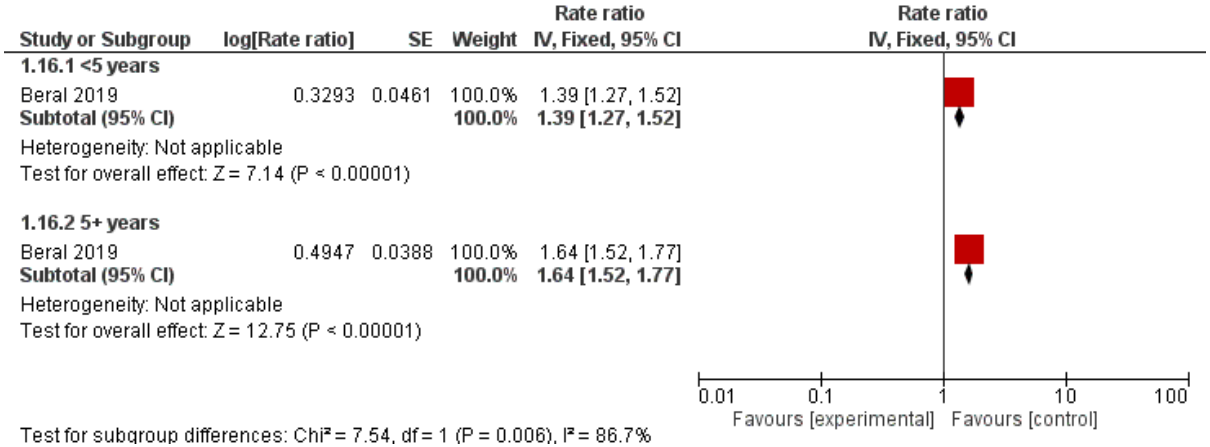


Figure 14: Mortality from breast cancer, current user, by duration of use

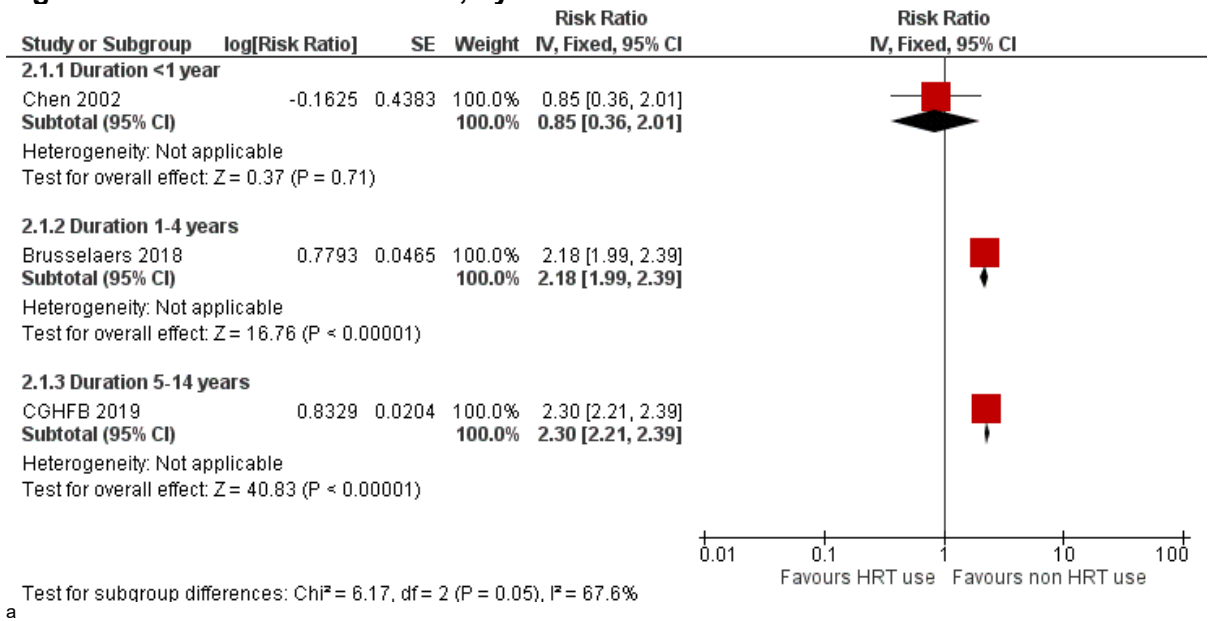


1

Comparison 2: Continuous combined oestrogen and progestogen versus no HRT

Incidence of breast cancer

Figure 15: Current HRT users, by duration of use



[a]

[a] Brusselaers 2018 is an odds ratio, but presented under risk ratio in the forest plot for presentational purposes.

Comparison 3: Continuous combined oestrogen and progestogen versus placebo

Incidence of breast cancer

Figure 16: Ethnicity

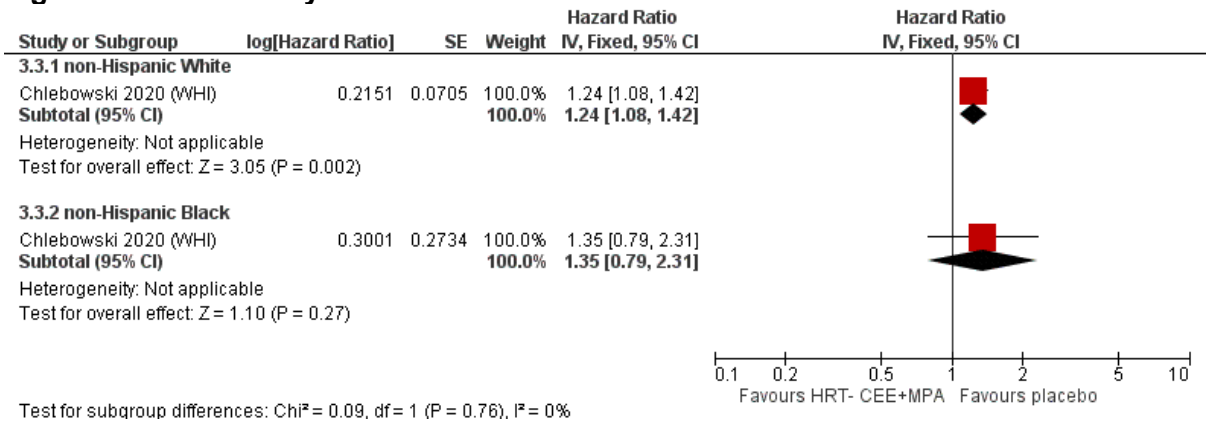
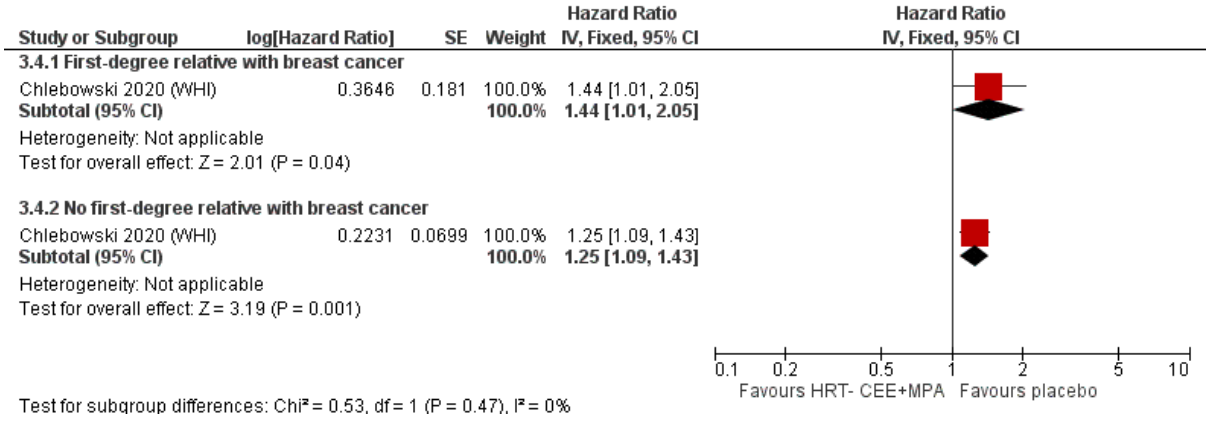


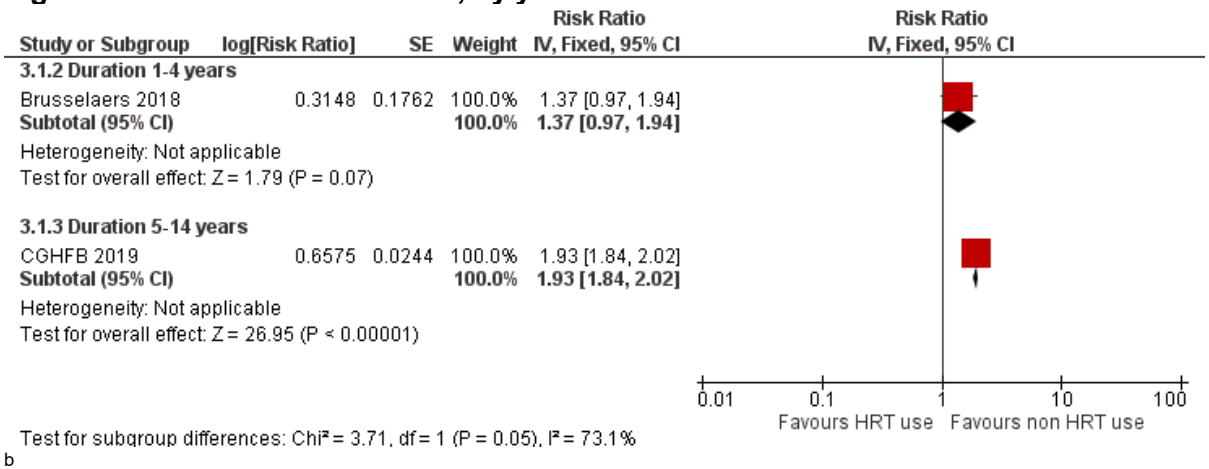
Figure 17: Family history



Comparison 4: Sequential combined oestrogen and progestogen versus no HRT

Incidence of breast cancer

Figure 18: Current HRT users, by years of use



[b]

[b] Brusselaers 2018 is an odds ratio, but presented under risk ratio in the forest plot for presentational purposes.

Comparison 5: Oestrogen-only versus no HRT

Incidence of breast cancer

Figure 19: Current HRT users, by years of use

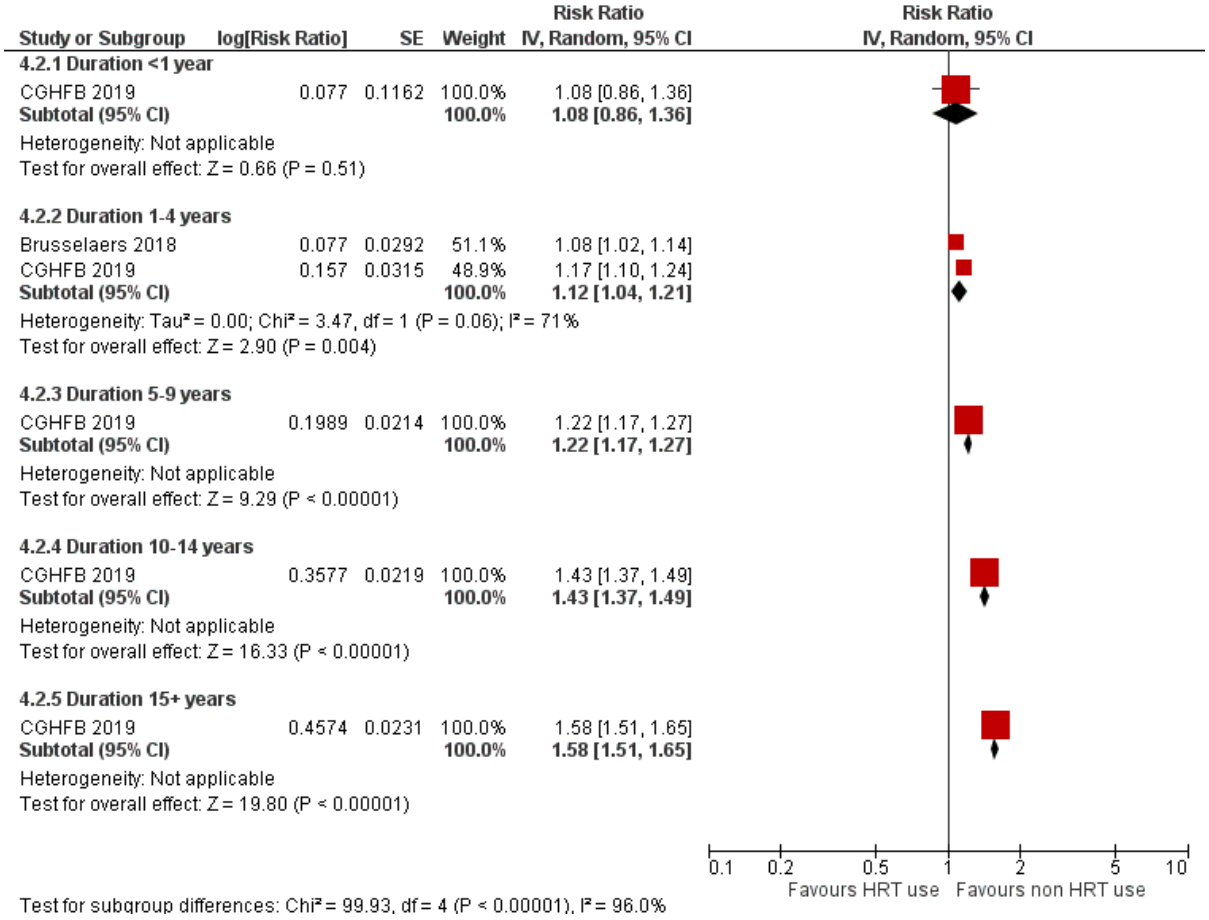
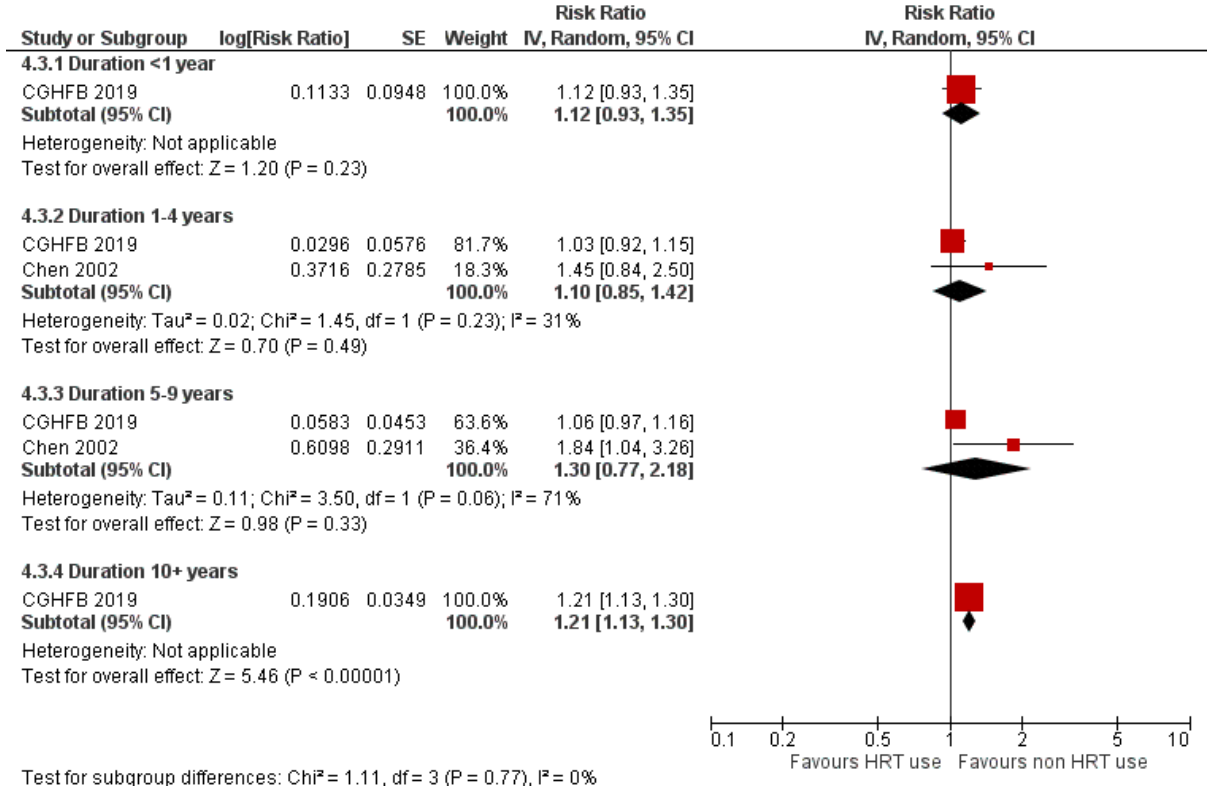


Figure 20: Past HRT users, <5 years since last use, by years of use



[c]

[c] Random effects model is presented in this forest plot for duration 5-9 years use. For duration 1-4 years random effect model is presented for presentational purpose only and a fixed effects model is used and presented in the GRADE table: RR 1.04 (0.94 to 1.17)

Figure 21: Past HRT users, 5-9 years since last use, by years of use

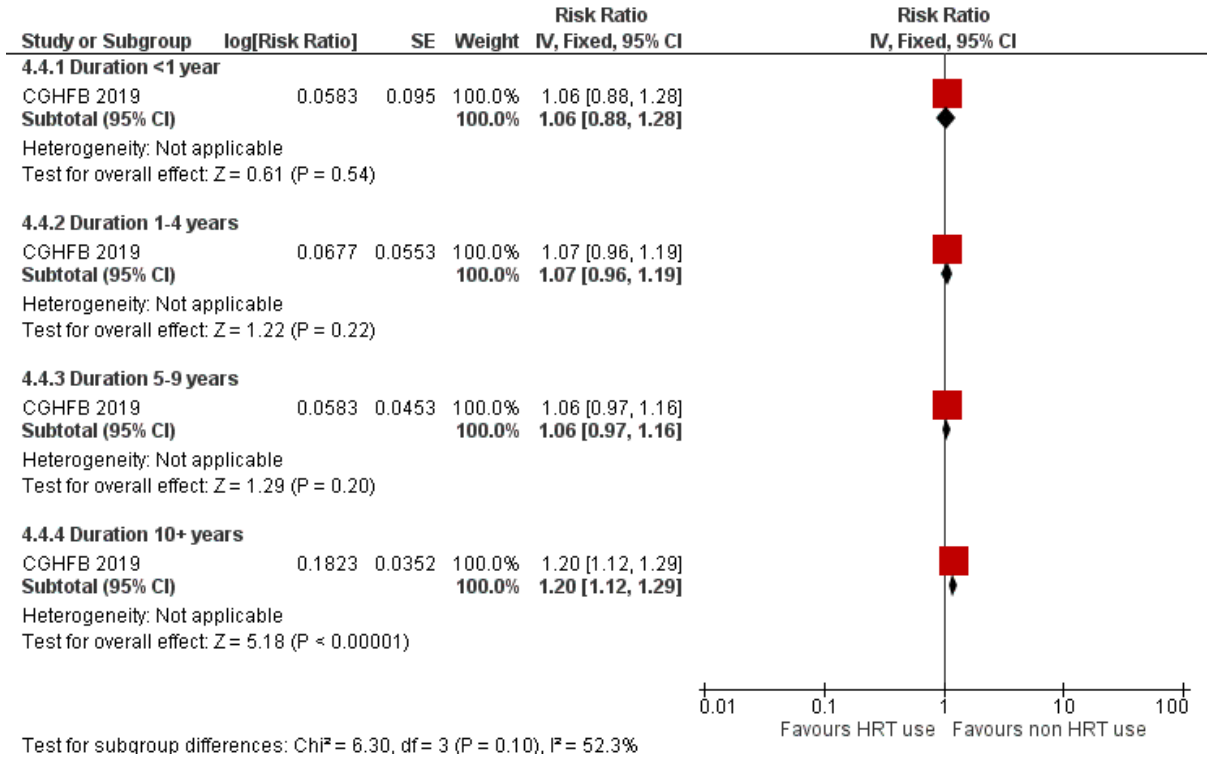


Figure 22: Past HRT users, 10+ years since last use, by years of use

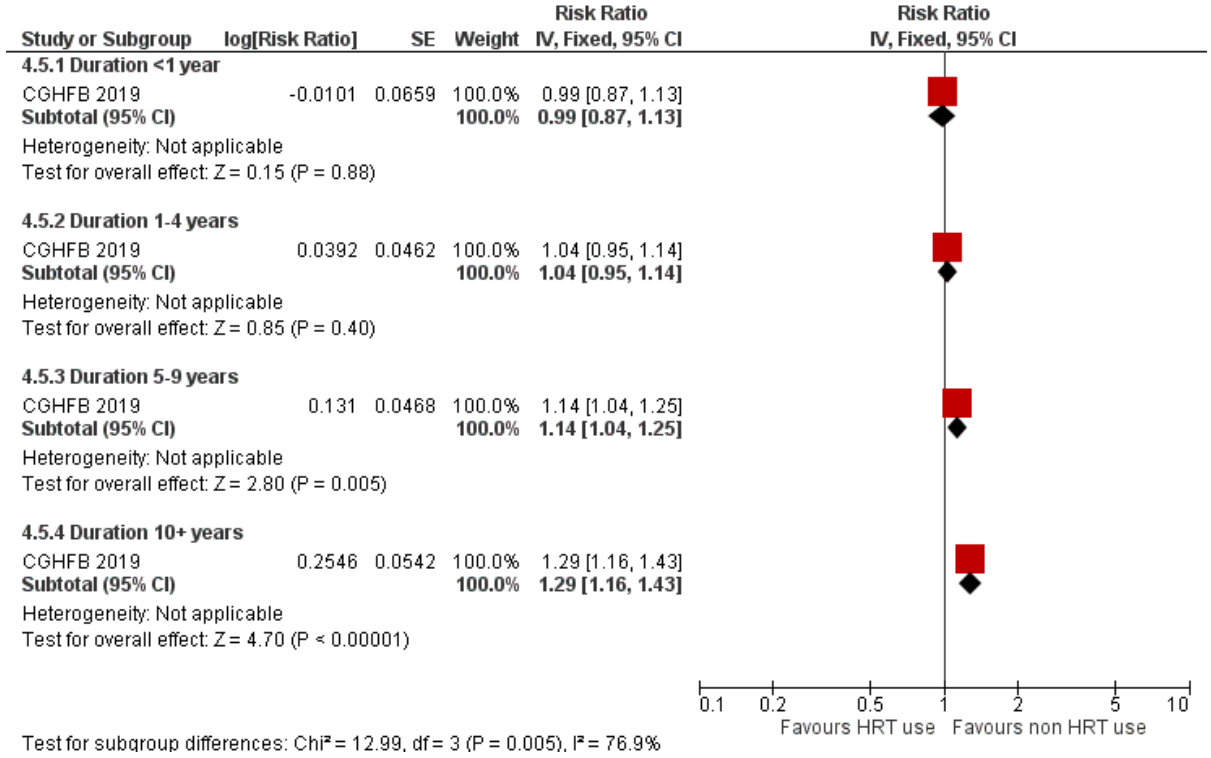


Figure 23: By constituent, for 1-4 years current use

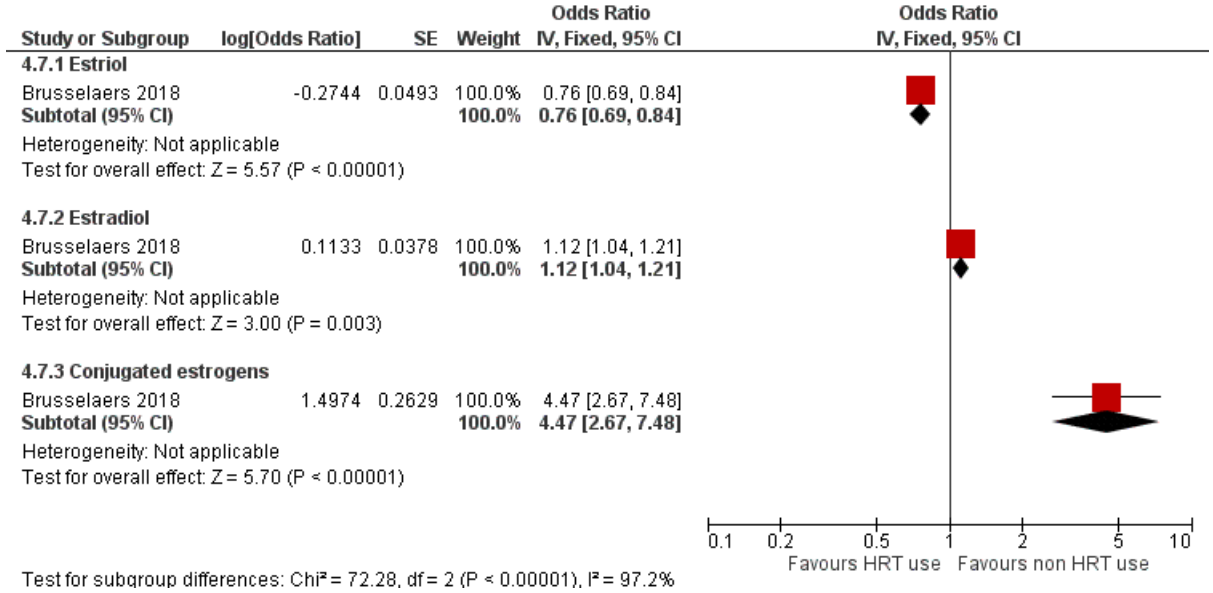


Figure 24: By constituent, for 5-14 years current use

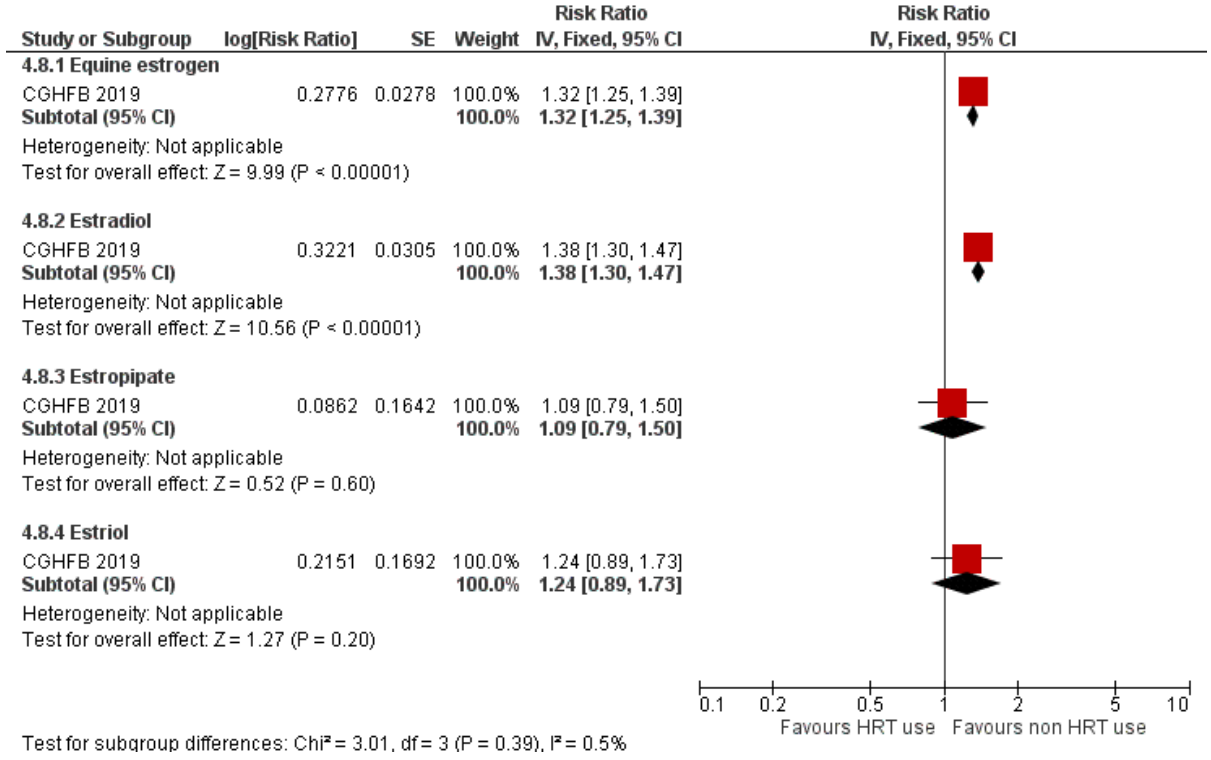


Figure 25: Age at first use, during 1-4 years current use

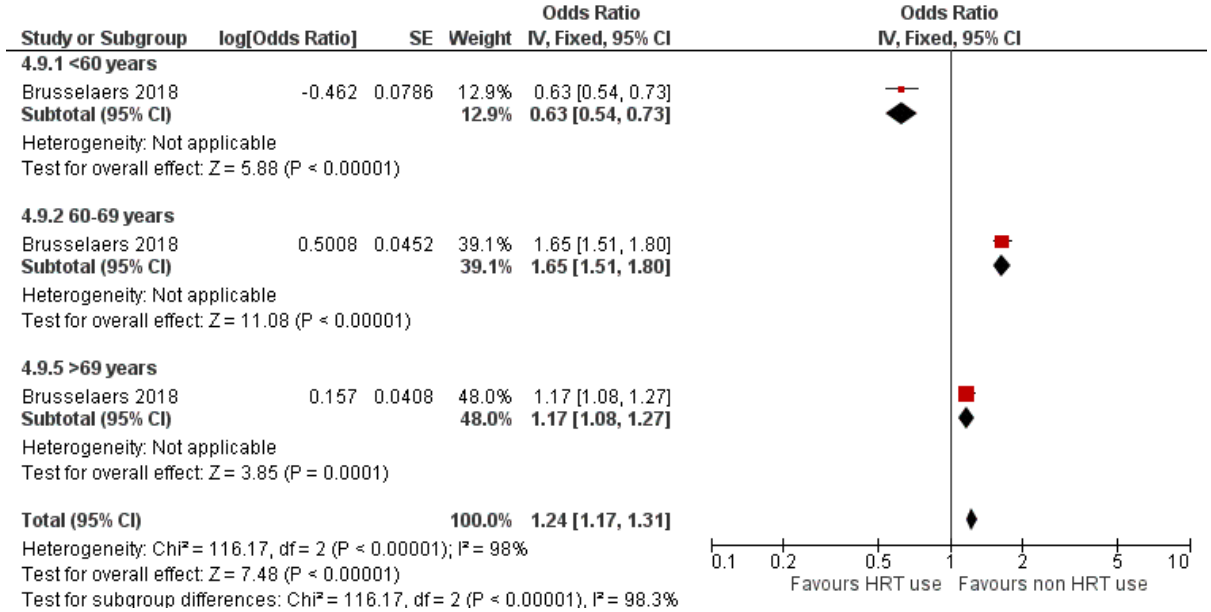


Figure 26: Age at first use, during 5-14 years current use

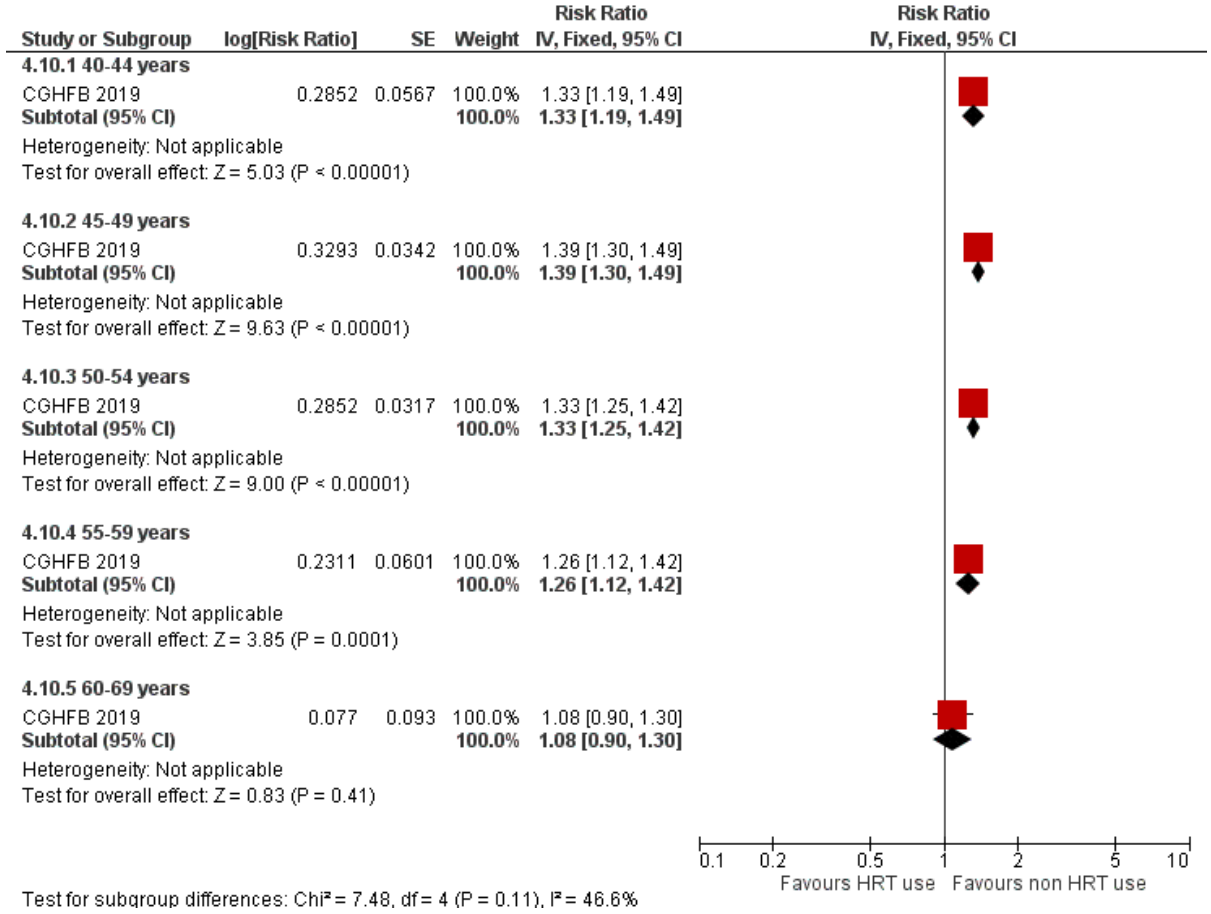


Figure 27: Mode of administration, for 1-4 years current use

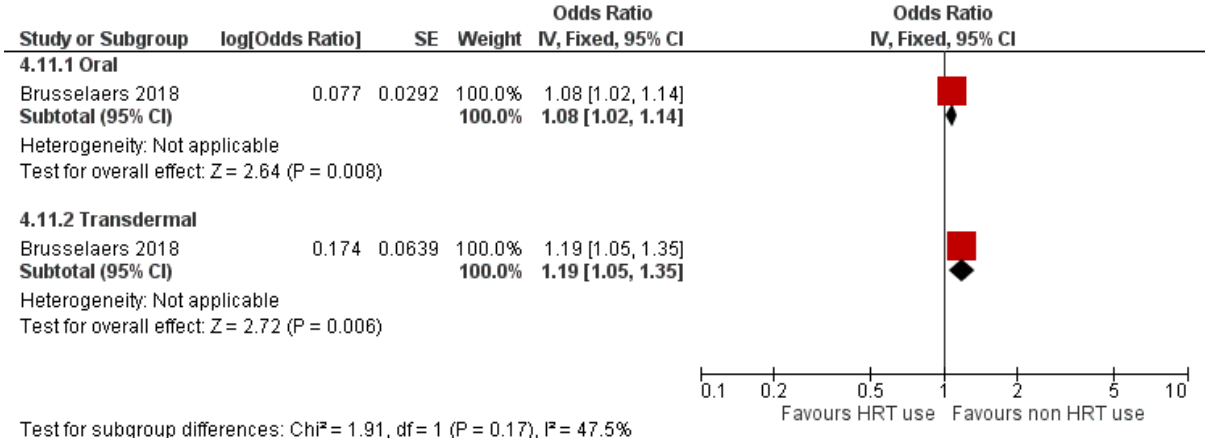


Figure 28: Mode of administration, for 5-14 years current use

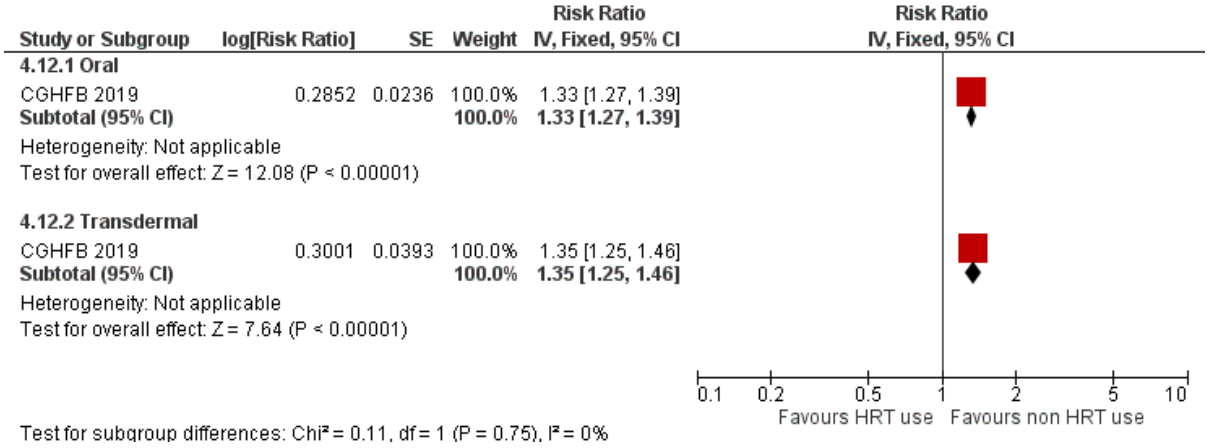


Figure 29: Time since menopause and first HRT use, for 5-14 years current use

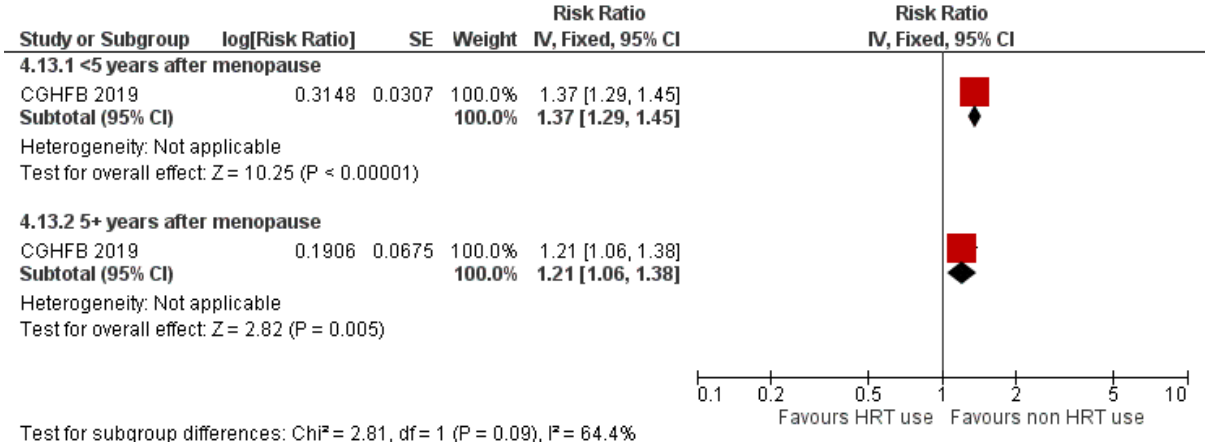


Figure 30: Family history of breast cancer, current use 5-14 years

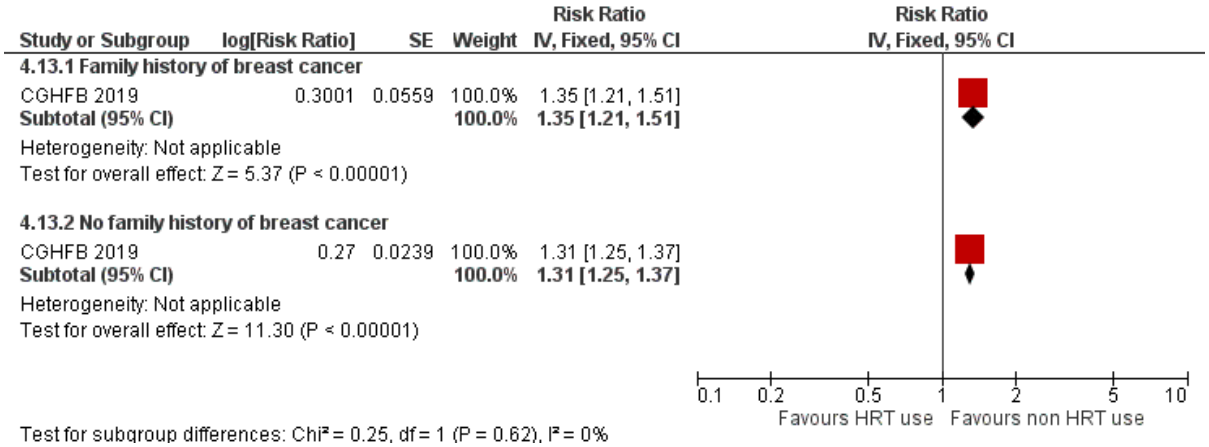


Figure 31: Ethnicity, current use 5-14 years

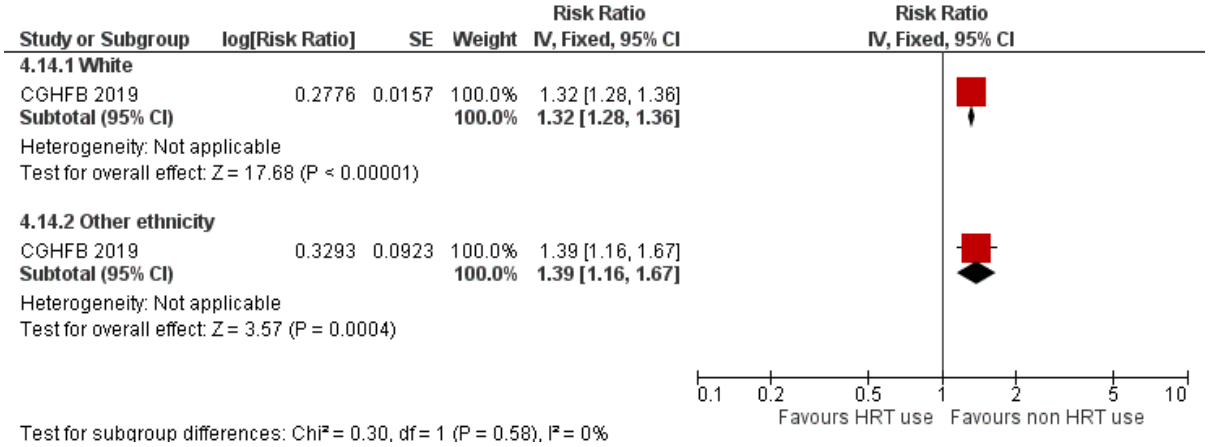
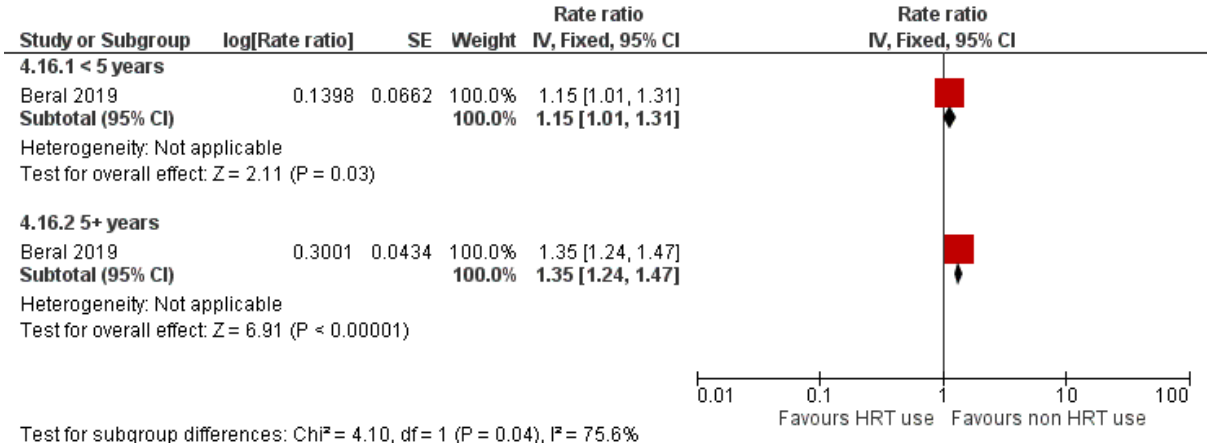
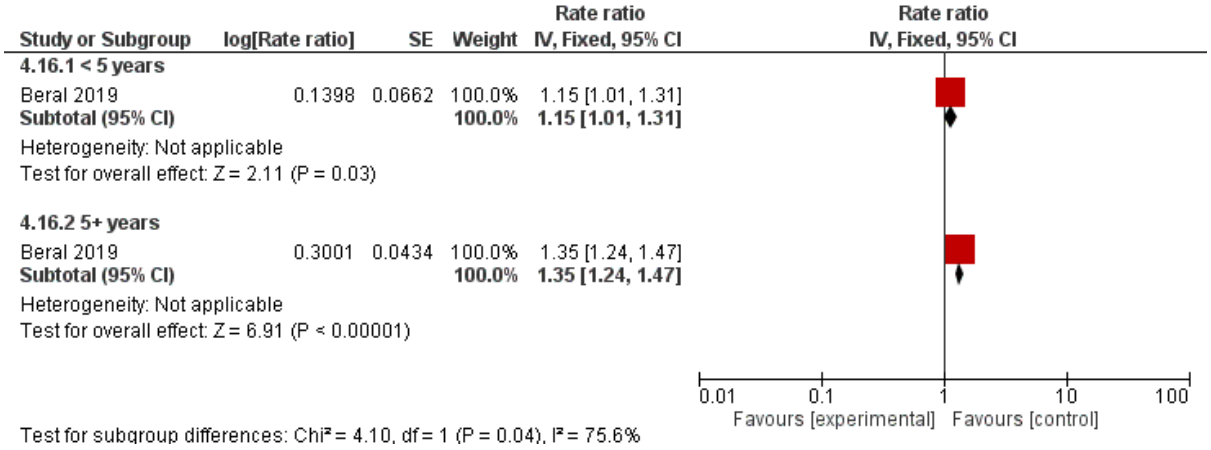


Figure 32: Education (proxy socioeconomic status), current use 5-14 years



1

Figure 33: Mortality from breast cancer, current user, by duration of use



1 **Comparison 6: Oestrogen-only versus placebo**

2 ***Incidence of breast cancer***

Figure 34: Ethnicity

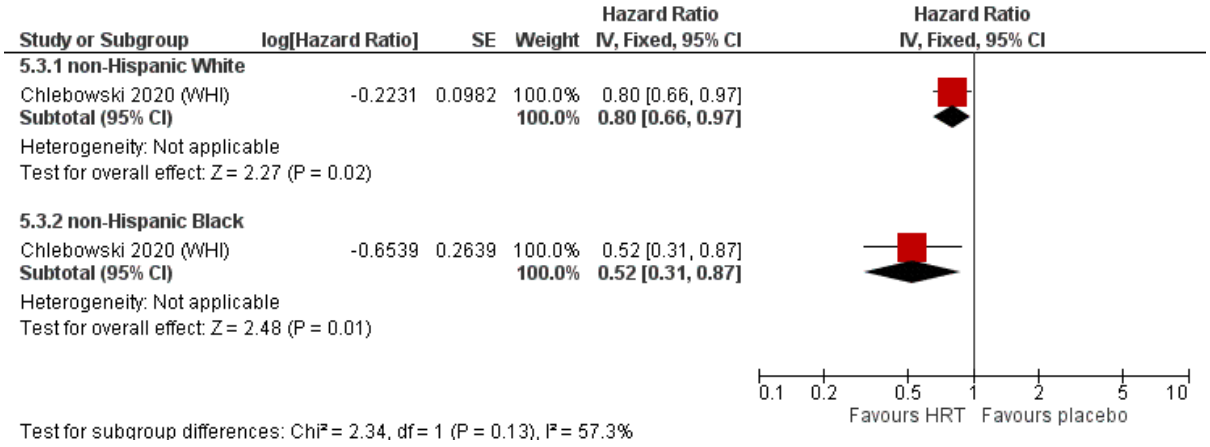
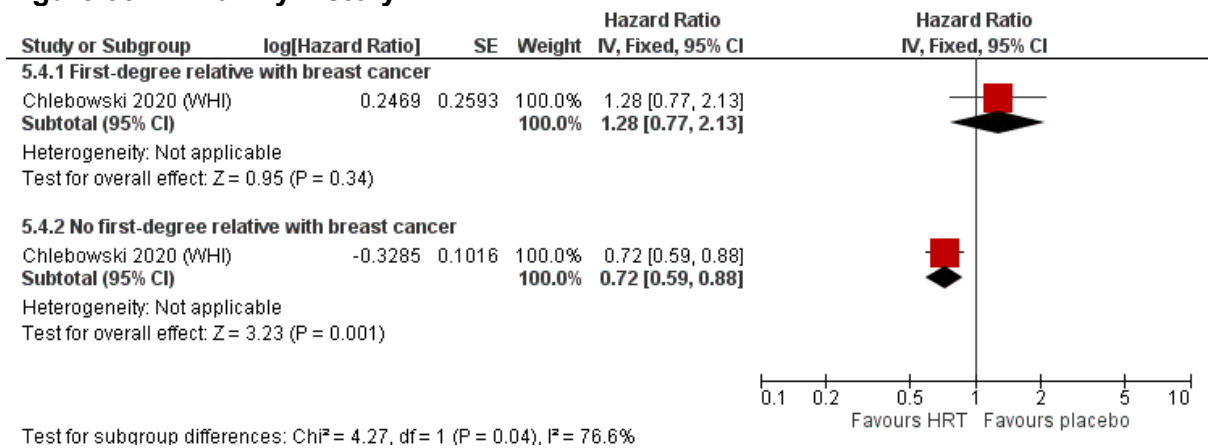


Figure 35: Family history



1

Appendix F GRADE tables

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

Table 4: Comparison 1: Any combined oestrogen and progestogen versus no HRT

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Incidence of invasive breast cancer												
Current HRT users, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.2 (1.01 to 1.43)	See Appendix L	MODERATE	CRITICAL
Duration 1-4 years												
2[2]	observational studies	serious[3]	very serious[4]	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.68 (1.53 to 1.86)	See Appendix L	VERY LOW	CRITICAL
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.97 (1.9 to 2.04)	See Appendix L	HIGH	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	not reported	not reported	RR 2.26 (2.16 to 2.36)	See Appendix L	HIGH	CRITICAL
Duration 15+ years												

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.51 (2.35 to 2.68)	See Appendix L	HIGH	CRITICAL
Past HRT users, <5 years since last use, by years of use												
Duration <1 year												
2[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1 (0.87 to 1.15)	See Appendix L	HIGH	CRITICAL
Duration 1-4 years												
2[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.18 (1.09 to 1.28)	See Appendix L	MODERATE	CRITICAL
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.21 (1.14 to 1.28)	See Appendix L	MODERATE	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.34 (1.25 to 1.44)	See Appendix L	MODERATE	CRITICAL
Past HRT users, 5-9 years since last use, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1 (0.89 to 1.12)	See Appendix L	HIGH	CRITICAL
Duration 1-4 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.06 (0.98 to 1.15)	See Appendix L	HIGH	CRITICAL

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.23 (1.15 to 1.32)	See Appendix L	MODERATE	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.28 (1.19 to 1.38)	See Appendix L	MODERATE	CRITICAL
Past HRT users, 10+ years since last use, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.06 (0.95 to 1.18)	See Appendix L	HIGH	CRITICAL
Duration 1-4 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.09 (1 to 1.19)	See Appendix L	HIGH	CRITICAL
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.19 (1.1 to 1.29)	See Appendix L	MODERATE	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.28 (1.15 to 1.42)	See Appendix L	MODERATE	CRITICAL
Age at first use, during 1-4 years current use												
<60 years												

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	OR 0.79 (0.73 to 0.87)	See Appendix L	LOW	CRITICAL
60-69 years												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 2.38 (2.22 to 2.55)	See Appendix L	MODERATE	CRITICAL
>69 years												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 3.59 (3.3 to 3.91)	See Appendix L	MODERATE	CRITICAL
Age at first use, during 5-14 years current use												
40-44 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.22 (1.96 to 2.51)	See Appendix L	HIGH	CRITICAL
45-49 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.14 (2.03 to 2.26)	See Appendix L	HIGH	CRITICAL
50-54 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.1 (2.01 to 2.19)	See Appendix L	HIGH	CRITICAL
55-59 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.97 (1.81 to 2.14)	See Appendix L	HIGH	CRITICAL

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
60-69 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.75 (1.48 to 2.07)	See Appendix L	HIGH	CRITICAL
Progestogenic constituent, for 5-14 years current use												
Levonorgestrel												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.12 (1.99 to 2.26)	See Appendix L	HIGH	CRITICAL
Norethisterone acetate												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.2 (2.09 to 2.32)	See Appendix L	HIGH	CRITICAL
Medroxyprogesterone acetate												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.07 (1.96 to 2.19)	See Appendix L	HIGH	CRITICAL
Micronised progesterone												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.05 (1.38 to 3.05)	See Appendix L	HIGH	CRITICAL
Dydrogesterone (synthetic progestogen/progestin)												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.41 (1.17 to 1.7)	See Appendix L	MODERATE	CRITICAL
Promegestone (synthetic progestogen/progestin)												

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 2.06 (1.19 to 3.57)	See Appendix L	MODERATE	CRITICAL
Nomegestrol acetate (synthetic progestogen/progestin)												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.38 (0.75 to 2.54)	See Appendix L	LOW	CRITICAL
Progesterone/dydrogesterone												
1 (Fournier 2014)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	HR 1.31 (1.15 to 1.49)	See Appendix L	MODERATE	CRITICAL
Family history of breast cancer, current use 5-14 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.11 (1.91 to 2.32)	See Appendix L	HIGH	CRITICAL
No family history of breast cancer, current use 5-14 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.02 (1.95 to 2.10)	See Appendix L	HIGH	CRITICAL
Education (proxy socioeconomic status), current use 5-14 years												
<13 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.28 (1.21 to 1.35)	See Appendix L	MODERATE	CRITICAL
13+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.35 (1.28 to 1.42)	See Appendix L	HIGH	CRITICAL
Time since menopause and first HRT use, for 5-14 years current use												

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
<5 years after menopause												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.12 (2.02 to 2.23)	See Appendix L	HIGH	CRITICAL
5+ years after menopause												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.77 (1.6 to 1.96)	See Appendix L	HIGH	CRITICAL
Ethnicity, current use 5-14 years												
White												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.32 (1.28 to 1.36)	See Appendix L	HIGH	CRITICAL
Other ethnicity												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.39 (1.16 to 1.67)	See Appendix L	MODERATE	CRITICAL
Mode of administration, for 1-4 years current use												
Oral												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 1.86 (1.77 to 1.95)	See Appendix L	MODERATE	CRITICAL
Transdermal												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	OR 1.4 (1.2 to 1.63)	See Appendix L	LOW	CRITICAL

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Mortality from breast cancer, current user, by duration of use												
<5 years												
1 (Beral 2019)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	557	3523	Rate ratio 1.39 (1.27 to 1.52)	Not calculable	MODERATE	CRITICAL
5+ years												
1 (Beral 2019)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	905	3523	Rate ratio 1.64 (1.52 to 1.77)	Not calculable	MODERATE	CRITICAL

CGHFB: Collaborative Group on Hormonal Factors in Breast; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio
1 95% CI crosses 1 MID
2 Brusselaers 2018; CGHFB 2019
3 Serious risk of bias in the evidence contributing to outcomes as assessed with ROBINS-I
4 Very serious heterogeneity unexplained by subgroup analysis
5 CGHFB 2019; Chen 2002
6 95% CI crosses 2 MID

Table 5: Comparison 2: Continuous combined oestrogen and progestogen versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Current HRT users, by duration of use												
Duration <1 year												
1 (Chen 2002)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	not reported	not reported	RR 0.85 (0.36 to 2.01)	See Appendix L	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Duration 1-4 years												
1 (Brusselaers 2018)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 2.18 (1.99 to 2.39)	See Appendix L	MODERATE	CRITICAL
Duration 5-14 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.3 (2.21 to 2.39)	See Appendix L	HIGH	CRITICAL
Past HRT users, <5 years since last use												
Duration 1-4 years												
1 (Chen 2002)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.85 (0.81 to 4.23)	See Appendix L	MODERATE	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio
1 95% CI crosses 2 MIDs
2 Serious risk of bias in the evidence contributing to outcomes as assessed with ROBINS-I
3 95% CI crosses 1 MID

Table 6: Comparison 3: Continuous combined oestrogen and progestogen versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progestogen	Placebo	Relative (95% CI)	Absolute		
Breast cancer incidence												
Overall												

1 (CGHFB 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	491/12664 (3.9%)	373/12255 (3%) 3%	RR 1.27 (1.12 to 1.45)	See Appendix L	MODERATE	CRITICAL
Ethnicity												
Non-Hispanic White												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	511/7141 (7.2%)	392/6805 (5.8%)	HR 1.24 (1.08 to 1.42)	not calculable	MODERATE	CRITICAL
Non-Hispanic Black												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	35/548 (6.4%)	28/574 (4.9%)	HR 1.35 (0.79 to 2.3)	not calculable	LOW	CRITICAL
Family history												
First-degree relative with breast cancer												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	94/1009 (9.3%)	62/895 (6.9%)	HR 1.44 (1.01 to 2.05)	not calculable	MODERATE	CRITICAL
No first-degree relative with breast cancer												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	457/7497 (6.1%)	359/7207 (5%)	HR 1.25 (1.09 to 1.45)	not calculable	MODERATE	CRITICAL
Mortality from breast cancer												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	71/8506 (0.83%)	53/8102 (0.65%)	HR 1.35 (0.94 to 1.94)	not calculable	MODERATE	CRITICAL

1 *CGHFB: Collaborative Group on Hormonal Factors in Breast; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; RR: risk ratio*
2 *1 95% CI crosses 1 MID*
3 *2 95% CI crosses 2 MIDs*

Table 7: Comparison 4: Sequential combined oestrogen and progestogen versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential combined oestrogen and progestogen	No HRT	Relative (95% CI)	Absolute		
Current HRT users, by duration of use												
Duration 1-4 years												
1 (Brusselaers 2018)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	not reported	not reported	OR 1.37 (0.97 to 1.94)	See Appendix L	LOW	CRITICAL
Duration 5-14 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.93 (1.84 to 2.02)	See Appendix L	HIGH	CRITICAL
Past HRT users, <5 years since last use												
Duration 1-4 years												
1 (Chen 2002)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	not reported	not reported	RR 1 (0.59 to 1.69)	See Appendix L	LOW	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; RR: risk ratio
1 Serious risk of bias in the evidence contributing to outcomes as assessed by ROBINS-I
2 95% CI crosses 2 MIDs

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
Incidence of invasive breast cancer												
Current HRT users – by years of use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.08 (0.86 to 1.36)	See Appendix L	MODERATE	CRITICAL
Duration 1-4 years												
2[2]	observational studies	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.12 (1.04 to 1.21)	See Appendix L	LOW	CRITICAL
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.22 (1.17 to 1.27)	See Appendix L	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	not reported	not reported	RR 1.43 (1.37 to 1.49)	See Appendix L	HIGH	CRITICAL
Duration 15+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.58 (1.51 to 1.65)	See Appendix L	HIGH	CRITICAL
Past HRT users, <5 years since last use, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.12 (0.93 to 1.35)	See Appendix L	MODERATE	CRITICAL
Duration 1-4 years												
2[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.04 (0.94 to 1.17)	See Appendix L	HIGH	CRITICAL
Duration 5-9 years												
2[5]	observational studies	no serious risk of bias	serious[4]	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.30 (0.77 to 2.18)	See Appendix L	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.21 (1.13 to 1.3)	See Appendix L	MODERATE	CRITICAL
Past HRT users, 5-9 years since last use, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.06 (0.88 to 1.28)	See Appendix L	MODERATE	CRITICAL
Duration 1-4 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.07 (0.96 to 1.19)	See Appendix L	HIGH	CRITICAL
Duration 5-9 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.06 (0.97 to 1.16)	See Appendix L	HIGH	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.2 (1.12 to 1.29)	See Appendix L	MODERATE	CRITICAL
Past HRT users, 10+ years since last use, by years of use												
Duration <1 year												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 0.99 (0.87 to 1.13)	See Appendix L	HIGH	CRITICAL
Duration 1-4 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.04 (0.95 to 1.14)	See Appendix L	HIGH	CRITICAL
Duration 5-9 years												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.14 (1.04 to 1.25)	See Appendix L	HIGH	CRITICAL
Duration 10+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.29 (1.16 to 1.43)	See Appendix L	MODERATE	CRITICAL
Past HRT users, unknown years since last use												
Duration <1 year												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 0.63 (0.6 to 0.66)	See Appendix L	MODERATE	CRITICAL
By constituent, for 1-4 years current use												
Oestriol												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	OR 0.76 (0.69 to 0.84)	See Appendix L	LOW	CRITICAL
Oestradiol												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 1.12 (1.04 to 1.21)	See Appendix L	MODERATE	CRITICAL
Conjugated oestrogens												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 4.47 (2.67 to 7.48)	See Appendix L	MODERATE	CRITICAL
By constituent, for 5-14 years current use												
Equine oestrogen												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.32 (1.25 to 1.39)	See Appendix L	MODERATE	CRITICAL
Oestradiol												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.38 (1.3 to 1.47)	See Appendix L	HIGH	CRITICAL
Estropipate												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.09 (0.79 to 1.5)	See Appendix L	LOW	CRITICAL
Oestriol												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.24 (0.89 to 1.73)	See Appendix L	MODERATE	CRITICAL
Age at first use, during 1-4 years current use												
<60 years												
1 (Brusselaers 2018)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 0.63 (0.54 to 0.73)	See Appendix L	MODERATE	CRITICAL
60-69 years												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.65 (1.51 to 1.8)	See Appendix L	MODERATE	
>69 years												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.17 (1.08 to 1.27)	See Appendix L	LOW	
Age at first use, during 5-14 years current use												
40-44 years												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.33 (1.19 to 1.49)	See Appendix L	MODERATE	CRITICAL
45-49 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.39 (1.3 to 1.49)	See Appendix L	HIGH	CRITICAL
50-54 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.33 (1.25 to 1.42)	See Appendix L	MODERATE	CRITICAL
55-59 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.26 (1.12 to 1.42)	See Appendix L	MODERATE	CRITICAL
60-69 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.08 (0.9 to 1.3)	See Appendix L	MODERATE	CRITICAL
Mode of administration, for 1-4 years current use												
Oral												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 1.08 (1.02 to 1.14)	See Appendix L	MODERATE	CRITICAL
Transdermal												
1 (Brusselaers 2018)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	OR 1.19 (1.05 to 1.35)	See Appendix L	LOW	CRITICAL
Mode of administration, for 5-14 years current use												
Oral												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.33 (1.27 to 1.39)	See Appendix L	HIGH	CRITICAL
Transdermal												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.35 (1.25 to 1.46)	See Appendix L	MODERATE	CRITICAL
Time since menopause and first HRT use, for 5-14 years current use												
<5 years after menopause												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.37 (1.29 to 1.45)	See Appendix L	HIGH	CRITICAL
5+ years after menopause												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.21 (1.06 to 1.38)	See Appendix L	MODERATE	CRITICAL
Family history, current use 5-14 years												
Family history of breast cancer												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.35 (1.21 to 1.50)	See Appendix L	MODERATE	CRITICAL
No family history of breast cancer												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.31 (1.25 to 1.37)	See Appendix L	MODERATE	CRITICAL
Ethnicity, current use 5-14 years												
White												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.32 (1.28 to 1.36)	See Appendix L	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen -only	No HRT	Relative (95% CI)	Absolute		
Other ethnicity												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.39 (1.16 to 1.67)	See Appendix L	MODERATE	CRITICAL
Education (proxy socioeconomic status), current use 5-14 years												
<13 years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	RR 1.28 (1.21 to 1.35)	See Appendix L	MODERATE	CRITICAL
13+ years												
1 (CGHFB 2019)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.35 (1.28 to 1.42)	See Appendix L	HIGH	CRITICAL
Mortality from breast cancer												
Current user, by duration of use												
<5 years												
1 (Beral 2019)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	Rate ratio 1.15 (1.01 to 1.31)	Not calculable	LOW	CRITICAL
5+ years												
1 (Beral 2019)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	not reported	not reported	Rate ratio 1.35 (1.24 to 1.47)	Not calculable	LOW	CRITICAL

1 *CGHFB: Collaborative Group on Hormonal Factors in Breast; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio*
2 *1 95% CI crosses 1 MID*
3 *2 Brusselaers 2018; CGHFB 2019*
4 *3 Serious risk of bias in the evidence contributing to outcomes as assessed with ROBINS-I*
5 *4 Serious heterogeneity unexplained by subgroup analysis*
6 *5 Chen 2002; CGHFB 2019*
7 *6 95% CI crosses 2 MIDs*

Table 9: Comparison 6: Oestrogen-only HRT versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conjugated equine oestrogen-only	Placebo	Relative (95% CI)	Absolute		
Incidence of invasive breast cancer												
Overall												
1 (CGHFB 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	188/6530 (2.9%)	246/6635 (3.7%)	RR 0.78 (0.64 to 0.94)	8 fewer per 1000 (from 2 fewer to 13 fewer)	MODERATE	CRITICAL
Ethnicity												
Non-Hispanic White												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	189/4009 (4.7%)	232/4075 (5.7%)	HR 0.80 (0.66 to 0.97)	not calculable	MODERATE	CRITICAL
Non-Hispanic Black												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24/781 (3.1%)	49/835 (5.9%)	HR 0.52 (0.31 to 0.88)	not calculable	MODERATE	CRITICAL
Family history												
First-degree relative with breast cancer												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	54/696 (7.8%)	45/685 (6.6%)	HR 1.28 (0.77 to 2.11)	not calculable	LOW	CRITICAL
No first-degree relative with breast cancer												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	168/4614 (3.6%)	228/4744 (4.8%)	HR 0.72 (0.59 to 0.89)	not calculable	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conjugated equine oestrogen-only	Placebo	Relative (95% CI)	Absolute		
Mortality from breast cancer; 20.7 years follow-up												
1 (Chlebowski 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30/6530 (0.46%)	46/6635 (0.69%)	HR 0.6 (0.37 to 0.97)	not calculable	MODERATE	CRITICAL

1 *CGHFB: Collaborative Group on Hormonal Factors in Breast; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; RR: risk ratio*
2 *1 95% CI crosses 1 MID*
3 *2 95% CI crosses 2 MIDs*

Appendix G Economic evidence study selection

Study selection for review question: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

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 for menopausal symptoms on the risk of developing breast cancer?

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

Appendix I Economic model

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

No economic analysis was conducted for this review question.

Appendix J Excluded studies

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

Excluded effectiveness studies

Study	Reason for exclusion
Abbasi, M.K., Fatima, M., Naval, A. et al. (2021) Breast pathology and cancer diagnosis: A link between Hormonal replacement therapy and breast cancer risk. Medical Forum Monthly 32(9): 100-104	- Intervention- oestrogen-only & combined HRT not reported separately
Abenhaim, Haim A, Suissa, Samy, Azoulay, Laurent et al. (2022) Menopausal Hormone Therapy Formulation and Breast Cancer Risk. Obstetrics and gynecology 139(6): 1103-1110	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Al-Shaibani,H., Bu-Alayyan,S., Habiba,S., Sorkhou,E., Al-Shamali,N., Al-Qallaf B (2006) Risk factors of breast cancer in Kuwait: Case-control study. Iranian Journal of Medical Sciences 31: 61-64	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Anderson, Garnet L, Limacher, Marian, Assaf, Annlouise R et al. (2004) Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291(14): 1701-12	- Already included in the CGHFB 2019 which is included in the review
Baek, J K, Kim, H I, Kang, M J et al. (2022) Relationship between the type of hormone replacement therapy and incidence of breast cancer in Korea. Climacteric : the journal of the International Menopause Society 25(5): 516-522	- Outcomes - relevant confounders not adjusted for - Only the statistical significance values adjusted for confounders - not the effect estimates
Bakken, Kjersti, Alsaker, Elin, Eggen, Anne Elise et al. (2004) Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. International journal of cancer 112(1): 130-4	- Cohort already included - Some women in this cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Bakken, Kjersti, Fournier, Agnes, Lund, Eiliv et al. (2011) Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. International journal of cancer 128(1): 144-56	- Cohort already included - Some women in this cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Barda, L, Nevler, A, Rosin, D et al. (2019) [THE EFFECTS OF HORMONAL REPLACEMENT THERAPY (HRT) ON MAMMOGRAPHIC BREAST DENSITY AND ABNORMAL MAMMOGRAMS PROMPTING FURTHER INVESTIGATION]. Harefuah 158(4): 239-243	- Language - Not in English
Beji, N K and Reis, N (2007) Risk factors for breast cancer in Turkish women: a hospital-based case-control study. European journal of cancer care 16(2): 178-84	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire

Study	Reason for exclusion
Beral, Valerie and Million Women Study, Collaborators (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet (London, England) 362(9382): 419-27	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Bergkvist,L., Adami,H.O., Persson,I., Hoover,R., Schairer,C. (1989) The risk of breast cancer after oestrogen and oestrogen-progestogen replacement. New England Journal of Medicine 321: 293-297	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Brinton, Louise A, Richesson, Douglas, Leitzmann, Michael F et al. (2008) Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study Cohort. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 17(11): 3150-60	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Byrne, Celia, Ursin, Giske, Martin, Christopher F et al. (2017) Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk. Journal of the National Cancer Institute 109(9)	- Outcomes - reported outcomes do not match the review protocols
Calle, Eugenia E, Feigelson, Heather Spencer, Hildebrand, Janet S et al. (2009) Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer 115(5): 936-45	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Calvocoressi, Lisa, Stowe, Meredith H, Carter, Darryl et al. (2012) Postmenopausal hormone therapy and ductal carcinoma in situ: a population-based case-control study. Cancer epidemiology 36(2): 161-8	- Outcomes - reported outcomes do not match the review protocols
Cherry, N, McNamee, R, Heagerty, A et al. (2014) Long-term safety of unopposed oestrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 121(6): 700-705	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Chiang, P.-H., Tang, F.-H., Tsai, E.-M. et al. (2019) Hormone therapy as risk factor of breast cancer modulated by diagnostic and lifestyle risk factors in Taiwan-A National Cohort study. Breast Journal 25(3): 531-534	- Outcomes - relevant confounders not adjusted for
Chlebowski,R.T., Hendrix,S.L., Langer,R.D., Stefanick,M.L., Gass,M., Lane,D., Rodabough,R.J., Gilligan,M.A., Cyr,M.G., Thomson,C.A., Khandekar,J., Petrovitch,H., McTiernan,A., Investigators W (2003) Influence of oestrogen plus progestogen on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 289: 3243-3253	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Chlebowski,R.T., Manson,J.E., Anderson,G.L., Cauley,J.A., Aragaki,A.K., Stefanick,M.L., Lane,D.S., Johnson,K.C., Wactawski-Wende,J.,	- Cohort already included

Study	Reason for exclusion
Chen,C., Qi,L., Yasmeen,S., Newcomb,P.A., Prentice R (2013) Estrogen plus progestogen and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. Journal of the National Cancer Institute 105: 526-535	Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Colditz, G A, Stampfer, M J, Willett, W C et al. (1992) Type of postmenopausal hormone use and risk of breast cancer: 12-year follow-up from the Nurses' Health Study. Cancer causes & control: CCC 3(5): 433-9	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Cordina-Duverger, Emilie, Truong, Therese, Anger, Antoinette et al. (2013) Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. PloS one 8(11): e78016	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Corrao, G, Zambon, A, Conti, V et al. (2008) Menopause hormone replacement therapy and cancer risk: an Italian record linkage investigation. Annals of oncology : official journal of the European Society for Medical Oncology 19(1): 150-5	- Comparison - not placebo or no HRT
Ellingjord-Dale, Merete, Vos, Linda, Tretli, Steinar et al. (2017) Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast cancer research: BCR 19(1): 10	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Ertz-Archambault, Natalie M, Rogoff, Lana B, Kosiorek, Heidi E et al. (2020) Depomedroxyprogesterone acetate therapy for hot flashes in survivors of breast cancer: no unfavorable impact on recurrence and survival. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 28(5): 2139-2143	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Ettinger, Bruce, Quesenberry, Charles, Schroeder, David A et al. (2018) Long-term postmenopausal oestrogen therapy may be associated with increased risk of breast cancer: a cohort study. Menopause (New York, N.Y.) 25(11): 1191-1194	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Ewertz, M (1988) Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. International journal of cancer 42(6): 832-8	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
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	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Fagerholm, Rainer, Faltinova, Maria, Aaltonen, Kirsi et al. (2018) Family history influences the tumor characteristics and prognosis of breast cancers developing during postmenopausal	- Intervention- oestrogen-only & combined HRT not reported separately

Study	Reason for exclusion
hormone therapy. Familial cancer 17(3): 321-331	
Fernandez, Esteve, Gallus, Silvano, Bosetti, Cristina et al. (2003) Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. International journal of cancer 105(3): 408-12	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Fletcher, A S, Erbas, B, Kavanagh, A M et al. (2005) Use of hormone replacement therapy (HRT) and survival following breast cancer diagnosis. Breast (Edinburgh, Scotland) 14(3): 192-200	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Folsom, A R, Mink, P J, Sellers, T A et al. (1995) Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. American journal of public health 85(8pt1): 1128-32	- Intervention- oestrogen-only & combined HRT not reported separately
Fornili, M, Perduca, V, Fournier, A et al. (2021) Association between menopausal hormone therapy, mammographic density and breast cancer risk: results from the E3N cohort study. Breast cancer research: BCR 23(1): 47	- Outcomes - reported outcomes do not match the review protocols
Fournier, Agnes; Berrino, Franco; Clavel-Chapelon, Francoise (2008) Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast cancer research and treatment 107(1): 103-11	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Fournier, Agnes, Berrino, Franco, Riboli, Elio et al. (2005) Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. International journal of cancer 114(3): 448-54	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Godina, Christopher, Ottander, Erik, Tryggvadottir, Helga et al. (2020) Prognostic Impact of Menopausal Hormone Therapy in Breast Cancer Differs According to Tumor Characteristics and Treatment. Frontiers in oncology 10: 80	- Intervention- oestrogen-only & combined HRT not reported separately
Grodstein, F, Stampfer, M J, Colditz, G A et al. (1997) Postmenopausal hormone therapy and mortality. The New England journal of medicine 336(25): 1769-75	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Hedblad, Bo, Merlo, Juan, Manjer, Jonas et al. (2002) Incidence of cardiovascular disease, cancer and death in postmenopausal women affirming use of hormone replacement therapy. Scandinavian journal of public health 30(1): 12-9	- Intervention- oestrogen-only & combined HRT not reported separately
Hulley, Stephen, Furberg, Curt, Barrett-Connor, Elizabeth et al. (2002) Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 288(1): 58-66	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting

Study	Reason for exclusion
Hvidtfeldt, Ulla Arthur, Lange, Theis, Andersen, Ingelise et al. (2013) Educational differences in postmenopausal breast cancer--quantifying indirect effects through health behaviors, body mass index and reproductive patterns. PloS one 8(10): e78690	- Intervention- oestrogen-only & combined HRT not reported separately
Jernstrom, Helena, Bendahl, Par-Ola, Lidfeldt, Jonas et al. (2003) A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: the women's health in the Lund area (WHILA) study (Sweden). Cancer causes & control: CCC 14(7): 673-80	- Cohort already included - Women in the cohort (South Swedish tumour Registry) have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Jiang, Yi; Xie, QinLi; Chen, Rong (2022) Breast Cancer Incidence and Mortality in Relation to Hormone Replacement Therapy Use Among Postmenopausal Women: Results From a Prospective Cohort Study. Clinical breast cancer 22(2): e206-e213	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Jordan, V Craig (2020) Molecular Mechanism for Breast Cancer Incidence in the Women's Health Initiative. Cancer prevention research (Philadelphia, Pa.) 13(10): 807-816	- Study design - not a systematic review, randomised controlled trial, or observational study
Kauppila A (1995) The use of oestrogens and progestogen and the risk of breast cancer in post-menopausal women. G.A. Colditz et al. N. Engl. J. Med. 1995; 332: 1589- 93. Pharmacological Research 32: 327	- Study design - comment piece
Kerlikowske, Karla, Miglioretti, Diana L, Ballard-Barbash, Rachel et al. (2003) Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 21(23): 4314-21	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire (women attending screening at indication of a radiologist)
Kim, Sohyun, Ko, Yeonsook, Lee, Hwa Jeong et al. (2018) Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. Breast cancer research and treatment 170(3): 667-675	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire - Systematic review. Included studies checked for relevance, most excluded due to study design. Relevant included studies are already included as part of the Lancet 2019 publication
Kjartansdottir, Olof J, Sigurdardottir, Lara G, Olafsdottir, Elinborg J et al. (2017) Estrogen-progestin use and breast cancer characteristics in lean and overweight postmenopausal women. Breast cancer research and treatment 163(2): 363-373	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Lando, J F; Heck, K E; Brett, K M (1999) Hormone replacement therapy and breast cancer risk in a nationally representative cohort. American journal of preventive medicine 17(3): 176-80	- Intervention- oestrogen-only & combined HRT not reported separately
Lee, Sulggi, Kolonel, Laurence, Wilkens, Lynne et al. (2006) Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. International journal of cancer 118(5): 1285-91	- Cohort already included

Study	Reason for exclusion
	Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Leventea, Eleni, Harkness, Elaine F, Brentnall, Adam R et al. (2021) Is Breast Cancer Risk Associated with Menopausal Hormone Therapy Modified by Current or Early Adulthood BMI or Age of First Pregnancy?. Cancers 13(11)	- Outcomes - reported outcomes do not match the review protocols (invasive cancer reported combined with in situ)
Li, Christopher I, Daling, Janet R, Haugen, Kara L et al. (2014) Use of menopausal hormone therapy and risk of ductal and lobular breast cancer among women 55-74 years of age. Breast cancer research and treatment 145(2): 481-9	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Liu, James H, Black, Denise R, Larkin, Lisa et al. (2020) Breast effects of oral, combined 17beta-estradiol, and progesterone capsules in menopausal women: a randomized controlled trial. Menopause (New York, N.Y.) 27(12): 1388-1395	- Outcomes - reported outcomes do not match the review protocols
Lund, Eiliv, Bakken, Kjersti, Dumeaux, Vanessa et al. (2007) Hormone replacement therapy and breast cancer in former users of oral contraceptives--The Norwegian Women and Cancer study. International journal of cancer 121(3): 645-8	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Lyytinen, Heli; Pukkala, Eero; Ylikorkala, Olavi (2009) Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstetrics and gynecology 113(1): 65-73	- Comparison - Not placebo or no HRT users. Comparison group cases were calculated from national statistics
Manjer, J, Malina, J, Berglund, G et al. (2001) Increased incidence of small and well-differentiated breast tumours in post-menopausal women following hormone-replacement therapy. International journal of cancer 92(6): 919-22	- Intervention- oestrogen-only & combined HRT not reported separately
Manson, JoAnn E, Chlebowski, Rowan T, Stefanick, Marcia L et al. (2013) Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310(13): 1353-68	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Marttunen, M B, Hietanen, P, Pyrhonen, S et al. (2001) A prospective study on women with a history of breast cancer and with or without oestrogen replacement therapy. Maturitas 39(3): 217-25	- Outcomes - relevant confounders not adjusted for
Mastorakos, G, Iatrakis, G, Zervoudis, S et al. (2021) Progestins and the Risk of Breast Cancer. Acta endocrinologica (Bucharest, Romania: 2005) 17(1): 90-100	- Study design - not a systematic review, randomised controlled trial, or observational study
Mikkola, Tomi S, Savolainen-Peltonen, Hanna, Tuomikoski, Pauliina et al. (2016) Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish	

Study	Reason for exclusion
nationwide comparative study. Menopause (New York, N.Y.) 23(11): 1199-1203	- Comparison. Mortality in HRT user is compared to an age-matched female population, which also included HRT users, and no adjustments made for appropriate confounders. - Therefore, this study did not meet the review protocol comparator requirement of 'no HRT' or 'placebo'
Mills, P K, Beeson, W L, Phillips, R L et al. (1989) Prospective study of exogenous hormone use and breast cancer in Seventh-day Adventists. Cancer 64(3): 591-7	- Intervention- oestrogen-only & combined HRT not reported separately
Mudhune, Godfrey H; Armour, Mike; McBride, Kate A (2019) Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: A systematic review and meta-analysis. Breast (Edinburgh, Scotland) 47: 43-55	- Intervention- oestrogen-only & combined HRT not reported separately - Systematic review checked for relevant studies: Some included studies did not report HRT oestrogen or combined oestrogen and progestogen separately. Some included studies did not adjust for confounders. One study O'Meara 2001 included
Newcomb,P.A., Titus-Ernstoff,L., Egan,K.M., Trentham-Dietz,A., Baron,J.A., Storer,B.E., Willett,W.C., Stampfer M (2002) Postmenopausal oestrogen and progestogen use in relation to breast cancer risk. Cancer Epidemiology, Biomarkers and Prevent 11: 593-600	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Newcomer, Laura M, Newcomb, Polly A, Potter, John D et al. (2003) Postmenopausal hormone therapy and risk of breast cancer by histologic type (United States). Cancer causes & control : CCC 14(3): 225-33	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Nozaki, Masahiro, Koera, Keiko, Nagata, Hideaki et al. (2004) Hormone replacement therapy and breast cancer risk in Kyushu University Hospital: supporting the Women's Health Initiative study. The journal of obstetrics and gynaecology research 30(4): 297-302	- Comparison - not placebo or no HRT
Pasco, Julie A, Kotowicz, Mark A, Henry, Margaret J et al. (2009) Health outcomes associated with hormone therapy in Australian women. Current drug safety 4(3): 169-72	- Intervention- oestrogen-only & combined HRT not reported separately
Persson, I, Thurfjell, E, Bergstrom, R et al. (1997) Hormone replacement therapy and the risk of breast cancer. Nested case-control study in a cohort of Swedish women attending mammography screening. International journal of cancer 72(5): 758-61	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Poggio, Francesca, Del Mastro, Lucia, Bruzzone, Marco et al. (2022) Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. Breast cancer research and treatment 191(2): 269-275	- Intervention- oestrogen-only & combined HRT not reported separately - Outcomes - relevant confounders not adjusted for
Porch,J.V., Lee,I.M., Cook,N.R., Rexrode,K.M., Burin J (2002) Estrogen-progestogen replacement therapy and breast cancer risk: the	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included

Study	Reason for exclusion
Women's Health Study (United States). Cancer Causes and Control 13: 847-854	in the review therefore not included separately to avoid double counting
Rossouw,J.E., Anderson,G.L., Prentice,R.L., Lacroix,A.Z., Kooperberg,C., Stefanick,M.L., Jackson,R.D., Beresford,S.A.A., Howard,B.V., Johnson,K.C., WHI study. Kotchen,J.M., Ockene J (2002) Risks and benefits of oestrogen plus progestogen in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. Journal of the American Medical Association 288: 321-333	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Rueda Beltz, C, Rojas Figueroa, A, Hinestroza Antolinez, S et al. (2021) Effects of progestogens used in menopause hormone therapy on the normal breast and benign breast disease in postmenopausal women. Climacteric: the journal of the International Menopause Society 24(3): 236-245	- Outcomes - reported outcomes do not match the review protocols
Saether, Sarah; Bakken, Kjersti; Lund, Eiliv (2012) The risk of breast cancer linked to menopausal hormone therapy. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 132(11): 1330-4	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Sandvei, Marie Softeland, Vatten, Lars J, Bjelland, Elisabeth Krefting et al. (2019) Menopausal hormone therapy and breast cancer risk: effect modification by body mass through life. European journal of epidemiology 34(3): 267-278	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Salagame, Usha, Banks, Emily, O'Connell, Dianne L et al. (2018) Menopausal Hormone Therapy use and breast cancer risk by receptor subtypes: Results from the New South Wales Cancer Lifestyle and EvaluAtion of Risk (CLEAR) study. PloS one 13(11): e0205034	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Santen, Richard J, Heitjan, Daniel F, Gompel, Anne et al. (2020) Underlying Breast Cancer Risk and Menopausal Hormone Therapy. The Journal of clinical endocrinology and metabolism 105(6)	- Study design - not a systematic review, randomised controlled trial, or observational study - Secondary analysis extrapolating data from Lancet 2019 publication
Saxena, Tanmai, Lee, Eunjung, Henderson, Katherine D et al. (2010) Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 19(9): 2366-78	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Schairer, C, Lubin, J, Troisi, R et al. (2000) Menopausal oestrogen and oestrogen-progestin replacement therapy and breast cancer risk. JAMA 283(4): 485-91	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Schierbeck, Louise Lind, Rejnmark, Lars, Tofteng, Charlotte Landbo et al. (2012) Effect of	- Cohort already included

Study	Reason for exclusion
hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ (Clinical research ed.) 345: e6409	- Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Schuurman, A G; van den Brandt, P A; Goldbohm, R A (1995) Exogenous hormone use and the risk of postmenopausal breast cancer: results from The Netherlands Cohort Study. Cancer causes & control : CCC 6(5): 416-24	- Intervention- oestrogen-only & combined HRT not reported separately
Sellers, T A, Mink, P J, Cerhan, J R et al. (1997) The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. Annals of internal medicine 127(11): 973-80	- Intervention- oestrogen-only & combined HRT not reported separately
Shufelt, Chrisandra, Bairey Merz, C Noel, Pettinger, Mary B et al. (2018) Estrogen-alone therapy and invasive breast cancer incidence by dose, formulation, and route of delivery: findings from the WHI observational study. Menopause (New York, N.Y.) 25(9): 985-991	- Comparison - not placebo or no HRT
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 - HRT not oestrogen-only, or combined oestrogen and progestogen
Sourander, L, Rajala, T, Raiha, I et al. (1998) Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). Lancet (London, England) 352(9145): 1965-9	- Outcomes - reported outcomes do not match the review protocols
Stahlberg, Claudia, Lynge, Elsebeth, Andersen, Zorana Jovanovic et al. (2005) Breast cancer incidence, case-fatality and breast cancer mortality in Danish women using hormone replacement therapy--a prospective observational study. International journal of epidemiology 34(4): 931-5	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Stahlberg, Claudia, Pedersen, Anette Tonnes, Lynge, Elsebeth et al. (2004) Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. International journal of cancer 109(5): 721-7	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Tjonneland, Anne, Christensen, Jane, Thomsen, Birthe L et al. (2004) Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: a prospective Danish cohort study. Cancer 100(11): 2328-37	- Outcomes - reported outcomes do not match the review protocols
Toti, A, Agugiaro, S, Amadori, D et al. (1986) Breast cancer risk factors in Italian women: a multicentric case-control study. Tumori 72(3): 241-9	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Vickers, Madge R, MacLennan, Alastair H, Lawton, Beverley et al. (2007) Main morbidities recorded in the women's international study of	- Cohort already included

Study	Reason for exclusion
long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. BMJ (Clinical research ed.) 335(7613): 239	Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Wang, Shao-Ming, Pfeiffer, Ruth M, Gierach, Gretchen L et al. (2020) Use of postmenopausal hormone therapies and risk of histology- and hormone receptor-defined breast cancer: results from a 15-year prospective analysis of NIH-AARP cohort. Breast cancer research: BCR 22(1): 129	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Wang, Tengteng, Bradshaw, Patrick T, Moorman, Patricia G et al. (2020) Menopausal hormone therapy use and long-term all-cause and cause-specific mortality in the Long Island Breast Cancer Study Project. International journal of cancer 147(12): 3404-3415	- Study design - data on HRT use are collected after the outcome of interest is known by self-reported questionnaire
Willis, D B, Calle, E E, Miracle-McMahill, H L et al. (1996) Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. Cancer causes & control: CCC 7(4): 449-57	- Cohort already included - Women in the cohort have already been included under CGHFB 2019, which is included in the review therefore not included separately to avoid double counting
Yang, Zhilan, Hu, Ying, Zhang, Jing et al. (2017) Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: a systematic review and meta-analysis. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 33(2): 87-92	- Outcomes - reported outcomes do not match the review protocols - Systematic review, included studies checked for relevance. Most studies included in the Lancet 2019 which is included in this review. Other studies not included due to no relevant outcomes, or data on HRT not collected at time of prescription, or relevant confounders not adjusted for.
Yoo, Tae-Kyung, Han, Kyung Do, Kim, DaHye et al. (2020) Hormone Replacement Therapy, Breast Cancer Risk Factors, and Breast Cancer Risk: A Nationwide Population-Based Cohort. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 29(7): 1341-1347	- Intervention- oestrogen-only & combined HRT not reported separately
Zeng, Zexian, Jiang, Xia, Li, Xiaoyu et al. (2018) Conjugated equine oestrogen and medroxyprogesterone acetate are associated with decreased risk of breast cancer relative to bioidentical hormone therapy and controls. PloS one 13(5): e0197064	- Outcomes - relevant confounders not adjusted for
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 - HRT not oestrogen-only, or combined oestrogen and progestogen - Intervention is levonorgestrel-releasing intrauterine system

Excluded economic studies

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

Appendix K Research recommendations – full details

There are overarching research recommendations related to all health outcomes addressed in this guideline update (including breast 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.

K.1.1 Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

Research recommendation

Do different types of progestogens (for example, micronised progesterone) alter the risk of breast cancer, endometrial cancer and cardiovascular disease?

Why this is important

Current evidence suggests that the risk of breast and endometrial cancer for HRT users is greater than for those who do not use HRT. However, there is insufficient evidence on the types of progestogens in HRT preparations and the risk of breast cancer and endometrial cancer. Understanding whether the risks differ between preparations will enable those considering taking HRT for menopausal symptoms to be more informed of any risks that may be associated with the use of different HRT preparations.

Rationale for research recommendation

Table 10: Research recommendation rationale

Importance to 'patients' or the population	Women with troublesome vasomotor symptoms may be offered HRT. However, HRT may increase the risk of breast and endometrial cancer. There are different preparations of HRT with newer types of progestogens available. It is uncertain whether the risk of breast or endometrial cancer differs between the different types of progestogen. Data from large observational studies are required to better inform optimum HRT regimens to inform women about the risks, if any, associated with different types of progestogen.
Relevance to NICE guidance	Progestogens have been considered in this guideline, however there was insufficient evidence to draw conclusions of the effects of different types of progestogens, for example micronised progesterone. Research in this area is essential to inform future updates of key recommendations in the guideline
Relevance to the NHS	The outcome would affect what types of progestogens are offered for HRT for troublesome vasomotor symptoms which is provided by the NHS, the counselling women receive before commencing treatment and informed choice by patients.
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	It is established that continuous combined HRT containing synthetic progestogen for 4-5 years increases breast cancer risk. It is uncertain whether up to 5 years of micronised progesterone also increases breast cancer risk. It is also uncertain whether the risk of endometrial cancer differs if combined HRT preparations contain synthetic progestogens or micronised progesterone. The HRT regimen (continuous combined vs sequential) may also affect risk of breast and endometrial cancers, with sequential regimens (with less progestogen exposure) conferring less risk of breast or endometrial cancer than continuous combined regimens.
Equality considerations	Women in minority ethnic groups are not well represented in studies relating to HRT use or menopause. The risks associated with HRT may differ among different ethnic groups.

HRT: hormone replacement therapy

Modified PICO table

Table 11: Research recommendation modified PICO table

Population	Women, non-binary and trans people with troublesome vasomotor symptoms (including perimenopause and postmenopause)
Intervention	Combined HRT including oestrogen and micronised progesterone, or synthetic progesterone such as: • Dydrogesterone • Medroxyprogesterone • Norethisterone • Levonorgestrel
Comparator	Interventions compared to each other or placebo / no HRT
Outcomes	• Incidence of endometrial cancer • Mortality from endometrial cancer • Incidence of invasive breast cancer • Mortality from breast cancer
Study design	Observational study designs where data on HRT use are collected before the outcome of interest is known as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies
Timeframe	Short and long term
Additional information	None

HRT: hormone replacement therapy

Appendix L Absolute risk tables and calculations

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

Absolute risks were calculated according to age group. For certain subgroups (age at first use; constituent; family history; education; time since menopause and first HRT use; ethnicity; mode of administration) it was not possible to calculate the absolute risks due to lack of information on their background risks.

Table 12: Number of breast cancer cases with no use, current use and past use of combined HRT in people who, if they used it, started HRT at 50 and used it for 5 years

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	12	13	15	19	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who started HRT at 50 and used it for 5 years	21 (current user)	16 (past user)	19 (past user)	23 (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	59
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 50 and used it for 5 years	Not applicable	Not applicable	Not applicable	Not applicable	79

In Table 12, based on age at starting (50 years old) and duration of use (5 years), people aged 50 to 54 were current users of HRT at the time the data was collected, and had used HRT for under 5 years.

Table 13: Number of breast cancer cases with no use, current use and past use of combined HRT in people who, if they used it, started HRT at 50 and used it for 10 years

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	12	13	15	19	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who started HRT at 50 years old and used it for 10 years	21 (current user)	26 (current user)	20 (past user)	25 (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	59

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 50 years old and used it for 10 years	Not applicable	Not applicable	Not applicable	Not applicable	92

In Table 13, based on age at starting (50 years old) and duration of use (10 years), people aged 50 to 59 were current users of HRT at the time the data was collected, and had used HRT for under 10 years.

Table 14: Number of breast cancer cases with no use, current use and past use of oestrogen-only HRT in people who, if they used it, started HRT at 50 and used it for 5 years

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	12	13	15	19	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who started HRT at 50 and used it for 5 years	14 (current user)	17 (past user) NS	16 (past user) NS	22 (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	59
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 50 and used it for 5 years	Not applicable	Not applicable	Not applicable	Not applicable	69

In Table 14, NS means that the difference between a figure for HRT users and the corresponding figure for non-HRT users is non-significant.

In Table 14, based on age at starting (50 years old) and duration of use (5 years), people aged 50 to 54 were current users of HRT at the time the data was collected, and had used HRT for under 5 years.

Table 15: Number of breast cancer cases with no use, current use and past use of oestrogen-only HRT in people who, if they used it, started HRT at 50 years old and used it for 10 years

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
Number of breast cancer cases over a 5-year period per 1000 people who never used HRT	12	13	15	19	Not applicable
Number of breast cancer cases over a 5-year period per 1000 people who	14 (current user)	16 (current user)	18 (past user)	23 (past user)	Not applicable

	50-54 years old	55-59 years old	60-64 years old	65-69 years old	50–69 years old
started HRT at 50 and used it for 10 years					
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	59
Cumulative number of breast cancer cases over a 20-year period per 1000 people who started HRT at 50 and used it for 10 years	Not applicable	Not applicable	Not applicable	Not applicable	71

In Table 15, based on age at starting (50 years old) and duration of use (10 years), people aged 50 to 59 were current users of HRT at the time the data was collected, and had used HRT for under 10 years.

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

See Supplement 19 for calculations.