National Institute for Health and Care Excellence

Final

Menopause (update)

[E] Endometrial cancer

NICE guideline NG23

Evidence review underpinning recommendations 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point) and 1.8.1 and 1.8.2, as well as the statements related to endometrial cancer in tables 1 and 2 (with related absolute numbers) in the NICE guideline

November 2024

Final

This evidence review was developed by NICE

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Endometrial cancer

Review question

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

Introduction

Unopposed oestrogen HRT increases the risk of endometrial cancer in women with a uterus due to the way oestrogen stimulates abnormal growth of the endometrium. As a result, women with a uterus who take HRT typically receive combined oestrogen and progesterone therapy to balance the effects on the endometrium. This review aimed to quantify the endometrial cancer risk associated with the different types of HRT and to examine whether different types of combined HRT are effective in reducing the increased risk of endometrial cancer.

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 post-menopause)

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 endometrial cancer • Mortality from endometrial 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

Twenty studies reported in 27 publications were included for this review, 11 observational studies (Allen 2010, Bakken 2004, Beral 2005, Fournier 2014, Gambrell 1979, Holm 2018, Liang 2021, Morch 2016, Schneider 2009, Sponholtz 2018 and Trabert 2013) and 9 randomised controlled trials (RCTs) reported in 16 publications (Byrjalsen 1999, Cherry 2002, Cherry 2014, Chlebowski 2016, Ferenczy 2002, Heiss 2008, Hulley 1998, Hulley 2002, Langer 2006, Manson 2013, Nachtigall 1979, Obel 1993, PEPI 1995, Prentice 2009, Prentice 2021, and Rossouw 2002).

Three RCTs were reported in multiple publications, with different outcomes, different follow-up or different subgroup analysis: the ESPRIT study (Cherry 2014, Cherry 2002), the HERS study (Hulley 1998, Hulley 2002) and the WHI study (Chlebowski 2016, Heiss 2008, Manson 2013, Prentice 2009, Prentice 2021, Rossouw 2002).

The included studies are summarised in Table 2.

Twelve studies compared oestrogen-only hormone replacement therapy (HRT) to placebo (2 RCTs reported in 3 publications: Cherry 2002, Cherry 2014 and PEPI 1995, and 9 observational studies: Bakken 2004, Beral 2005, Fournier 2014, Gambrell 1979, Holm 2018, Liang 2021, Morch 2016, Sponholtz 2018, Trabert 2013), and 27 publications compared combined oestrogen plus progestogens to placebo (9 RCTs in 16 publications: Byrjalsen 1999, Cherry 2002, Cherry 2014, Chlebowski 2016, Ferenczy 2002, Heiss 2008, Hulley 1998, Hulley 2002, Langer 2006, Manson 2013, Nachtigall 1979, Obel 1993, PEPI 1995, Prentice 2009, Prentice 2021, and Rossouw 2002, and 11 observational studies: Allen 2010, Bakken 2004, Beral 2005, Fournier 2014, Gambrell 1979, Holm 2018, Liang 2021, Morch 2016, Schneider 2009, Sponholtz 2018 and Trabert 2013).

One study was conducted in Canada (Ferenczy 2002), 1 study was conducted in China (Liang 2021), 4 studies were conducted in Denmark (Byrjalsen 1999, Holm 2018, Morch 2016, and Obel 1993), 1 study was conducted in various European countries (Allen 2010), 1 study was conducted in France (Fournier 2014), 1 study was conducted in Norway (Bakken 2004), 4 studies were conducted in the UK (Beral 2005, Cherry 2002, Cherry 2014, and Schneider 2009), 13 studies were conducted in the US (Chlebowski 2016, Gambrell 1979, Heiss 2008, Hulley 1998, Hulley 2002, Manson 2013, Nachtigall 1979, PEPI Writing Group 1995, Prentice 2009, Prentice 2021, Rossouw 2002, Sponholtz 2018, and Trabert 2013), and 1 study was conducted in the US and Europe (Langer 2006).

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 and duration and recency of HRT
Allen 2010 (EPIC) Prospective cohort study Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom	N=115474 Postmenopausal women without hysterectomy. Mean age (SD): • Never use: 58.7 years (6.2) • Former use: 57.7 years (5.1) • Current use: 54.6 years (4.9)	Combined oestrogen and progestogen HRT • Continuous • Sequential	No HRT	Incidence of endometrial cancer Duration • Any duration of use • <2 years • >2 years Recency: • Current users
Bakken 2004 (NOWAC) Prospective cohort study Norway	N=27621 Postmenopausal women aged 45-64 years. Mean age: 53, SD: NR	Oestrogen-only HRT Combined oestrogen and progestogen HRT: • Continuous • Sequential	No HRT	Incidence of endometrial cancer Duration • Any duration of use Recency: • All users
Beral 2005 (MWS) Prospective cohort study UK	N=716738 Postmenopausal women without hysterectomy. Mean age (SD): • Oestrogen and progestogen: 57 years (3.6) • Oestrogen-only: 57.1 years (4.1) • No HRT: 58 years (4.3)	Oestrogen-only HRT Combined oestrogen and progestogen HRT • Continuous	No HRT	Incidence of endometrial cancer Duration • Any duration of use • <5 years • ≥5 years Recency: • All users
Byrjalsen 1999 RCT Denmark	N=278 Postmenopausal women aged 45 to 63 years. Mean age: 53.4 years, SD: NR	Combined oestrogen and progestogen HRT • Sequential: 2mg/d oestradiol combined with 50µg or 25µg gestodene on days 17 to 28 • Sequential: 1mg/d oestradiol combined with 25µg gestodene on days 17 to 28 • Continuous	Placebo	Incidence of endometrial cancer Duration • 2 years Recency • Current users

Study	Population	Intervention	Comparison	Outcomes and duration and recency of HRT
Cherry 2002 (ESPRIT) RCT UK	N=1017 Postmenopausal women, aged 50–69 years who had survived a first myocardial infarction (27% and 21% with hysterectomy) Mean age: 62.6 years, SD: NR	Oestrogen-only HRT • Continuous: 2mg/d oestradiol valerate	Placebo	Incidence of endometrial cancer Duration • 2 years Recency • Current users
Cherry 2014 (ESPRIT) RCT UK	N=1017 Post-menopausal women aged 50–69 years who had survived a first myocardial infarction. Mean age: NR	Oestrogen-only HRT • 2mg/d oestradiol valerate	Placebo	Incidence of endometrial cancer Mortality from endometrial cancer Duration • 2 years Recency • Past users of 12.6 years (mean) recency
Chlebowski 2016 (WHI) RCT US	N=16608 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	Incidence of endometrial cancer Mortality from endometrial cancer Duration • 5.6 years (mean) Recency • Current and past users of 13.2 years cumulative follow-up
Ferenczy 2002 RCT Canada	N=579 Postmenopausal women aged 45–65 years without hysterectomy. Mean age: 55.6 years, SD: NR	Combined oestrogen and progestogen HRT • Sequential: 1mg/d oestradiol + 5mg or 10mg dydrogesterone on days 15 to 28 • Sequential: 2mg/d oestradiol + 10 or 20mg dydrogesterone on days 15 to 28	Placebo	Incidence of endometrial cancer Duration • 2 years Recency • Current users

Study	Population	Intervention	Comparison	Outcomes and duration and recency of HRT
Fournier 2014 (E3N) Prospective cohort study France	N=65630 Postmenopausal women aged 40-65 years. Mean age (SD): 64.2 (6.5) (overall age at diagnosis)	Oestrogen-only HRT Oestrogen and progestogen HRT	No HRT	Incidence of endometrial cancer Duration • Any duration of use Recency: • Current users
Gambrell 1979 Retrospective cohort study US	N=NR Postmenopausal women. Mean age: 57.3 years, SD NR	Oestrogen-only HRT Oestrogen + progestogen HRT	No HRT	Incidence of endometrial cancer Duration • ≥15 years Recency: • Current users
Heiss 2008 (WHI) RCT US	N=16608 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age: 63.2 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 5.6 years (mean) Recency • Past users of 3 years recency
Holm 2018 (DCHC) Prospective cohort study Denmark	N=29152 Postmenopausal women aged 50-64 years. Median age (5,95%): 56 (50-54)	Oestrogen-only HRT Oestrogen + progestogen HRT	No HRT	Incidence of endometrial cancer Duration • ≥15 years Recency: • Current users
Hulley 1998 (HERS) RCT US	N=2763 Postmenopausal women younger than 80 years with intact uterus and established coronary disease. Mean age: 66.7 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 4.1 years Recency • Current users
Hulley 2002 (HERS) RCT US	N=2763 Postmenopausal women younger than 80 years with intact uterus and	Combined oestrogen and progestogen HRT	Placebo	Incidence of endometrial cancer Duration • 6.8 years

Study	Population	Intervention	Comparison	Outcomes and duration and recency of HRT
	established coronary disease. Mean age: 66.7 years, SD: NR	• Continuous: 0.625mg/d CEE + 2.5 mg/d MPA		Recency • Current users
Langer 2006 (OPAL) RCT US & Europe	N=866 Postmenopausal women aged 45-79 years (83% and 84.6% with intact uterus) Age: 58.6 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 3 years Recency • Current users
Liang 2021 (PLCO) Prospective cohort study China	N=45203 Postmenopausal women without hysterectomy aged 55-74 years. Median age (IQR) • No HRT: 73 years (67–77) • Current users: 68 years (65–73)	Oestrogen-only HRT Oestrogen + progestogen HRT	No HRT	Incidence of endometrial cancer Duration • <1 year • 1-3 years • 3-5 years • 5-10 years • >10 years Recency: • All users
Manson 2014 (WHI) RCT US	N=16608 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age: 63.2 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 5.6 years (mean) Recency • Current users
Morch 2016 Prospective cohort study Denmark	N=914595 Women aged 15-79 years. Mean age (SD): NR	Oestrogen-only HRT Oestrogen and progestogen HRT • Continuous	No HRT	Incidence of endometrial cancer Duration • Any duration of use Recency: • Current users
Nachtigall 1979 RCT US	N=168 Postmenopausal women inpatients Mean age: 55.1 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 2.5mg/d conjugated	Placebo	Incidence of endometrial cancer Duration • 10 years (mean) Recency

Study	Population	Intervention	Comparison	Outcomes and duration and recency of HRT
		oestrogen + 10mg/d MPA		• Current users
Obel 1993 RCT Denmark	N=151 Postmenopausal women born between 1930 and 1933. Age: NR	Combined oestrogen and progestogen HRT • Continuous:2mg/d oestradiol + 1 mg/d NETA • Sequential: 2mg oestradiol for 12 days, 2 mg oestradiol + 1 mg NETA for 10 days, 1 mg oestradiol for 6 days	Placebo	Incidence of endometrial cancer Duration • 2 years Recency • Current users
PEPI Writing Group 1995 (PEPI) RCT US	N=596 women Postmenopausal women aged 45 to 64 years with a uterus. Mean age: 56.2 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA • Sequential: 0.625 mg/d CEE + 10 mg/d MPA for the first 12 days or 200 mg/d MP for the first 12 days Oestrogen-only HRT • Continuous: 0.625mg/d CEE	Placebo	Incidence of endometrial cancer Duration • 3 years Recency • Current users
Prentice 2009 (WHI) RCT US	N=15188 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age: 63.2 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 5.6 years (mean) Recency • Current users
Prentice 2021 (WHI) RCT US	N=5520 Postmenopausal women aged 50 to 59 years without hysterectomy. Mean age: 55.2 years, SD: NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 5.6 years (mean) Recency • Current users

Study	Population	Intervention	Comparison	Outcomes and duration and recency of HRT
Rossouw 2002 (WHI) RCT US	N=16608 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age: 63.3 years, SD NR	Combined oestrogen and progestogen HRT • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	Incidence of endometrial cancer Duration • 5.2 years (mean) Recency • Current users
Schneider 2009 Prospective cohort study UK	N=602 Postmenopausal women. Mean age (SD): 51.3 years (6.1)	Oestrogen-only HRT Combined oestrogen and progestogen HRT	No HRT	Incidence of endometrial cancer Duration • Any duration of use Recency: • All users
Sponholtz 2018 (BWHS) Prospective cohort study US	N=47555 Postmenopausal women without hysterectomy aged 21-69 years. Mean age (SD): • HRT use: 36.6 years (116.5) • No HRT: 39.2 years (170.8)	Oestrogen-only HRT Combined oestrogen and progestogen HRT	No HRT	Incidence of endometrial cancer Duration • Any duration of use • 1-4 years • ≥5 years Recency: • Current users
Trabert 2013 Prospective cohort study US	N=68419 Postmenopausal women. Mean age (SD): NR	Oestrogen-only HRT Combined oestrogen and progestogen HRT • Sequential	No HRT	Incidence of endometrial cancer Duration • Any duration of use • <10 years • ≥10 years Recency: • Current users

BWHS: Black Women's Health Study; CEE: conjugated equine oestrogens; DCHC: The Diet, Cancer, and Health cohort; E3N: Étude épidemiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ESPRIT: European/Australasian Stroke Prevention in Reversible Ischaemia Trial; HERS: Heart and Estrogen/progestin Replacement Study; HRT: hormone replacement therapy; IQR: interquartile range; MP: micronized progesterone; MPA: medroxyprogesterone acetate; mg/d: milligrams per day; MWS: Million Women Study; NETA: norethisterone acetate; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NOWAC: Norwegian Women and Cancer Study; NR: not reported; OPAL: Occupational support for Patients undergoing Arthroplasty of the Lower limb Trial; PEPI: Postmenopausal Estrogen/Progestin Interventions; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RCT: randomised controlled trial; SD: standard deviation; UK: United Kingdom; US: United States of America; WHI: Women's Health Initiative.

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 – Methods for further details.

Combined oestrogen and progestogen HRT versus placebo

For incidence of endometrial cancer, the RCT evidence shows an important benefit for combined HRT over placebo for current and past users with cumulative follow up at 13.2 years and 18 years (median). In current and past users with 5-9 years duration of HRT, at 13.2 years follow up, with a BMI ≥25, there is also an important benefit favouring combined HRT over placebo. The evidence suggesting benefit was of high or moderate quality, respectively.

However, overall, the RCT data shows no important difference on the incidence of endometrial cancer for combined oestrogen and progestogen when compared to placebo for:

- current users with 1-4 years duration or 4 years duration
  - sub-grouped by the oestrogenic constituent: equine oestrogen
  - sub-grouped by progestogenic constituents: medroxyprogesterone acetate and norethisterone acetate
  - sub-grouped by sequential dosage (with oestradiol or equine oestrogen)
- current users with 2- or 3-years duration
- current users with 5.6 years (mean) duration
- current and past users with cumulative follow up at 8.5 years (mean)
- current users with 1-4 years duration, when sub-grouped by the oestrogenic constituent oestradiol
- current users with 1-4 years duration, when sub-grouped by the progestogenic constituent micronized progesterone, and any synthetic progestin (gestodene and dydrogesterone)
- current users with 5-9 years duration, or at 6.8 years (mean) duration
- current and past users with 5-9 years duration, by ethnicity at 13.2 years follow up
- current users with10-14 years duration
- all users with 5-9 years duration and with <5 years since last use

For the outcome mortality from endometrial cancer, there is no important difference in current and past users, 5-9 years duration of combined HRT, when compared to placebo. This evidence is low in quality.

Combined oestrogen and progestogen versus no HRT

Overall, the observational evidence shows no important difference for incidence of endometrial cancer between combined HRT and no HRT, except some moderate quality evidence, in current users for a duration of >2, which showed an important harm increasing the risk of endometrial cancer. Some high-quality evidence showed an important harm increasing the risk of endometrial cancer with the use of micronized progesterone in combined HRT compared to no HRT in current users and any duration of use, but no other oestrogenic or progestogenic constituent shows an important difference. There were no important differences between combined HRT users and no HRT depending on BMI from the evidence in one study. However, evidence from another study showed when further sub-grouped by ethnicity, there was an important benefit of combined HRT for BMI ≥30 in an ethnically white population when compared to no HRT, and an important harm of combined HRT for BMI >25 in an ethnically white population. This evidence was of high quality, respectively. In a black population, very low-quality evidence showed there was no evidence of an important difference with BMI <30 or ≥30 for incidence of endometrial cancer.

Sequential or continuous combined oestrogen and progestogen versus no HRT

For combined HRT taken in a sequential dosage, there is some high-quality evidence suggesting an important harm in current users with ≥10 years of use when compared to no HRT. For combined HRT taken continuously, some evidence of high quality showed a benefit for current users with any duration of use, but other evidence of moderate quality showed no important difference between current users with any duration of use when compared to no HRT. There were no statistically significant subgroup differences for the subgroups by duration of use, constituent, or route of administration. Subgroup evidence by BMI showed that there was an important benefit for continuous combined HRT users with a BMI ≥30 on the incidence of endometrial cancer, but no evidence of an important difference in those with a BMI <25 or 25-29.

There was no observational evidence available for the outcome mortality from endometrial cancer.

Oestrogen-only versus placebo

Overall, RCT data shows no evidence of an important difference on incidence of endometrial cancer in oestrogen-only HRT (current users with 1-4 years duration and a recency of 10-14 years since last use) when compared to placebo. This was also observed in sub-groups by oestrogenic constituent. For mortality from endometrial cancer, RCT evidence suggests no evidence of an important difference in current users with 1-4 years duration and a recency of 10-14 years since last use, when compared to placebo. The evidence is low in quality and typically, evidence which showed no difference included few studies and had seriously imprecise findings, therefore they should not be taken as definitive evidence of no difference.

Oestrogen-only versus no HRT

On the other hand, overall, the observational evidence suggests an important harm with oestrogen-only HRT in current and all users over no HRT on incidence of endometrial cancer. This harm is apparent in subgroups of years of use (≥10 and ≥15 years duration), oestrogenic constituents (conjugated and non-conjugated oestrogen, and oestriol), and route of administration (oral and transdermal). However, there is no evidence of an important difference in current and all users with a duration of <10 years. Subgroup data on participants with a BMI <25 shows an important harm in a mixed and ethnically white population but isn't seen in BMI 25-30 in a mixed population. The important harm is present for participants with a BMI 25- <30 in an ethnically white population. In both populations, there is an important benefit for those with a BMI ≥30. There is an important harm, both BMI <30 and ≥30 in an ethnically black population. The quality of the observational evidence ranged from very low to high, with the evidence suggesting an important harm mostly being of a high or moderate quality. There was no observational evidence available for the outcome mortality from endometrial cancer.

See Appendix F for full GRADE tables and Appendix M for absolute risk tables.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of included economic evidence

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose incidence of endometrial cancer and mortality from endometrial cancer as the critical outcomes for this review because hormonal replacement therapy use may contribute to the risk of endometrial cancer. The committee agreed on various subgroup stratifications to investigate whether this occurs in certain groups.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as very low to high.

Most of the evidence was downgraded for imprecision around the effect estimate. There were also concerns about bias for some of the evidence mainly due to lack of blinding in the RCTs. In the observational evidence, there were some concerns about bias due to some missing data and 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. Some of the evidence was also downgraded for inconsistency due to high heterogeneity which was not resolved by subgroup analysis.

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).

Benefits and harms

The committee discussed the limitations in the RCT evidence, such as low event rates and studies reporting very low doses of progestogens given in addition to oestrogens in HRT (which may not be effective to prevent the incidence of endometrial cancer), which made it difficult to draw reliable conclusions. Furthermore, some studies included women without a uterus, and therefore no endometrium, meaning these people could not develop endometrial cancer. Therefore, the committee focused their discussions on the observational evidence and their own knowledge and experience, but also drew on the RCT evidence where possible.

Combined HRT

The committee noted that the RCT evidence and some of the observational studies grouped any combined HRT data together. They noted that in the context of endometrial cancer it is important to differentiate between continuous combined HRT and sequential combined HRT regimens in which the progestogenic constituent is taken either every day or for fewer than 10 days per month, respectively, for clinical applicability (see below for more explanation on sequential combined HRT). Therefore, the committee largely considered the observational data that separated by sequential combined and continuous combined HRT, and the RCTs that specified the regimen when making recommendations.

Continuous combined HRT

RCT

The committee discussed that there was some evidence from the Women's Health Initiative RCT showing a reduced risk of endometrial cancer at 13- and 18-years follow-up. They discussed that the data from shorter follow-up period of 8.5 years also showed lower numbers of women with endometrial cancer in the combined HRT group compared , although this was not statistically significant. The committee discussed that the recency of use would be somewhat unknown as some participants could have gone on to use HRT outside of the trial setting. However, they noted that adherence during the intervention period of the WHI for combined HRT was low, with 42% discontinuing use, therefore they might expect that discontinuation remained even after the end of the trial period. The committee discussed that strengths of the evidence in particular that the evidence came from randomised controlled trials, and therefore there were no concerns regarding bias by confounding.

Observational evidence

The committee discussed that there was mixed quality observational evidence that suggested a reduced risk of endometrial cancer for continuous combined HRT in current users with any duration of use, and in all users (current and past users) with <5 years of use when compared to no HRT. Evidence from one observational study suggested there was no difference in the incidence of endometrial cancers for all users with ≥5 years of use when compared to no HRT.

The committee drew on the observational evidence of oestrogen-alone HRT in people with a uterus (as discussed below), which showed that this is harmful since it increases the risk of endometrial cancer. Based on expertise they noted that progestogens counteract the adverse effect of oestrogens on the endometrium and so it is consistent with the evidence showing continuous combined HRT (where a progestogen is taken every day with oestrogen), decreases the risk of developing endometrial cancer.

Interpretation of RCT and observational evidence

The committee agreed that the evidence from RCTs and observational studies, along with their experiential knowledge supported a recommendation to inform people that continuous combined HRT reduces the risk of endometrial cancer.

Sequential combined HRT

RCT

The committee discussed that there was some evidence from RCTs showing no difference in the incidence of endometrial cancer between HRT and placebo, when the dosage of progestogens varied in the HRT arm. They agreed they could not draw meaningful

conclusions from this evidence as the studies were likely underpowered for the outcome endometrial cancer incidence and the event numbers were low.

Observational evidence

The committee discussed the duration of use for sequential combined HRT. They discussed that some observational evidence suggested an important harm for incidence of endometrial cancer with sequential combined HRT in current users with 10 or more years of use, but no difference in the risk with less than 10 years use. They concluded that the evidence supported a duration effect. The committee also discussed using experiential knowledge, that progestogens oppose the effect of oestrogen on the endometrium, and this occurs in a dose-dependent manner. Therefore, the protective effect of the progestogen in a sequential combined preparation is greater the more days per month that it is added to oestrogen.

The committee discussed the evidence, which suggested that sequential combined HRT may increase the incidence of endometrial cancer. The committee agreed that the constituent and dose of the combined HRT affects the risk of endometrial cancer (including duration of use, doses and days of progestogen per cycle, and higher oestrogen dose). This should be explained to the person so that they can make an informed choice when considering HRT for menopause symptoms.

Type of progestogen, BMI and ethnicity

The committee also discussed other parts of the evidence showing important differences, such as type of progestogen, BMI and ethnicity. They noted that confidence intervals were wide (suggesting studies were underpowered or had low event rates) and whilst there were some differences compared to no HRT the overlap in confidence intervals showed that there was uncertainty in whether one of the results was superior to another. They therefore decided not to comment on this but encouraged further research (see below).

Oestrogen-only HRT

RCT

The committee discussed that there was limited RCT evidence on oestrogen-only HRT, with only two studies that had no or few cases of endometrial cancer. They agreed that they could not draw any meaningful conclusions from the data from the RCTs.

Observational evidence

The committee therefore discussed the observational evidence for oestrogen-only HRT versus no HRT, which suggested an increased risk of incidence of endometrial cancer in current and all users (current and past users) at ≥10 and ≥15 years duration, in both oral and transdermal HRT. The committee agreed that the evidence could inform a recommendation that oestrogen-only HRT increases the risk of endometrial cancer for people with a uterus.

Starting HRT

The committee discussed the observational evidence showing that oestrogen-only HRT increases the incidence of endometrial cancer in people with a uterus (see above). This is consistent with their expert knowledge that oestrogen alone, if given to people with an intact uterus, can stimulate the growth of the uterine lining (endometrium). In turn, this oestrogen stimulation can lead to an increased risk of endometrial hyperplasia (overgrowth of the endometrium) and potentially, endometrial cancer. Adding progesterone to the HRT regimen helps protect the endometrium by counteracting the stimulating effects of oestrogen, reducing the risk of endometrial issues. They therefore recommended (as is current standard practice) that if a person decides that they want to take HRT for menopause symptoms

people with a uterus should be offered combined oestrogen and progestogen whereas people who have had a total hysterectomy should be offered oestrogen alone.

The committee discussed that this may be different for people with a sub-total hysterectomy. They decided that they could not be prescriptive about the type of HRT to be used for people who have had a sub-total hysterectomy because their condition is clinically complex, and they had not reviewed evidence about the effect of HRT on risk of endometrial cancer for this group. They acknowledged that people who were going to have, or had had, a sub-total hysterectomy would likely be under the care of a specialist who could discuss HRT options tailored to their needs.

Some people have a hysterectomy for a condition that may be affected by HRT, such as endometriosis. The committee did not review evidence related to such conditions. However, they recognised that the decision about the type of HRT that best balances benefits and risks for the person may be affected by that condition. For this reason, advice from a healthcare professional with specialist knowledge of that condition may be needed.

Research recommendation

The committee noted a finding related to ethnicity that they could not clearly comment on. This relates to the overall uncertainty around a lack of research recruiting people from minority ethnic backgrounds. They therefore made an overarching research recommendation to encourage more research in the effects of HRT on health outcomes (including endometrial cancer) in people from minority ethnic backgrounds (see appendix K of evidence report C).

There was a lack of evidence specifically relating to trans and non-binary people. The committee discussed that the recommendations could be generalised to trans men and non-binary people registered female at birth who have never taken cross sex hormones as gender affirming therapy. However, 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 cross sex hormones as gender affirming therapy. Therefore, the committee decided to add a research recommendation addressing this lack of evidence. The descriptions of the research recommendation 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 risk of HRT and endometrial 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 around combined HRT for people with a uterus and oestrogen-only for people without a uterus is standard practice and match recommendations from the previous guideline. There is unlikely to be an impact on resource use from these recommendations.

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 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.

While discussing the review evidence for incidence of endometrial cancer, the committee discussed the role of endometrial hyperplasia as a precursor to cancer. From their knowledge, the committee were aware that atypical hyperplasia may lead to a higher risk of cancer, whereas typical hyperplasia may hold a lower risk. The committee discussed RCT evidence from one study (PEPI 1995), which showed no increase in the incidence of endometrial cancer but found increased hyperplasia in the oestrogen-only HRT arm. The committee concluded that with a longer follow-up time, the study authors may have detected more endometrial cancers. This may have contributed to more evidence supporting the harmful link between oestrogen-only HRT and risk of endometrial cancer. Even though it was not an outcome listed in the protocol, it was one of the considerations that underpinned the recommendation stating that if a person decides that they want to take HRT for menopause symptoms people with a uterus should be offered combined oestrogen and progestogen (see the section related to starting HRT above).

The committee noted that the studies were all based on a population of post-menopausal women.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point) and 1.8.1, as well as the statements related to endometrial cancer in tables 1 and 2 (with the related absolute numbers tables) 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 1.5.32 – see evidence review C).

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

Allen 2010

Allen, Naomi E, Tsilidis, Konstantinos K, Key, Timothy J et al. (2010) Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. American journal of epidemiology 172(12): 1394-403

Bakken 2004

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

Beral 2005

Beral, Valerie, Bull, Diana, Reeves, Gillian et al. (2005) Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet (London, England) 365(9470): 1543-51

Byrjalsen 1999

Byrjalsen, I; Bjarnason, N H; Christiansen, C (1999) Progestational effects of combinations of gestodene on the postmenopausal endometrium during hormone replacement therapy. American journal of obstetrics and gynecology 180(3pt1): 539-49

Cherry 2002

Cherry, Nicola, Gilmour, Kyle, Hannaford, Philip et al. (2002) Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo-controlled trial. Lancet (London, England) 360(9350): 2001-8

Cherry 2014

Cherry, N, McNamee, R, Heagerty, A et al. (2014) Long-term safety of unopposed estrogen 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

Chlebowski 2016

Chlebowski, R T, Anderson, G L, Sarto, G E et al. (2016) Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. Journal of the National Cancer Institute 108(3)

Ferenczy 2002

Ferenczy, A, Gelfand, M M, van de Weijer, P H M et al. (2002) Endometrial safety and bleeding patterns during a 2-year study of 1 or 2 mg 17 beta-estradiol combined with sequential 5-20 mg dydrogesterone. Climacteric : the journal of the International Menopause Society 5(1): 26-35

Fournier 2014

Fournier, Agnes, Dossus, Laure, Mesrine, Sylvie et al. (2014) Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008. American journal of epidemiology 180(5): 508-17

Gambrell 1979

Gambrell Jr., R.D., Massey, F.M., Castaneda, T.A. et al. (1979) Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens. Journal of the American Geriatrics Society 27(9): 389-394

Heiss 2008

Heiss, G., Wallace, R., Anderson, G.L. et al. (2008) Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299(9): 1036-1045

Holm 2018

Holm, Marianne, Olsen, Anja, Kyro, Cecilie et al. (2018) The Influence of Menopausal Hormone Therapy and Potential Lifestyle Interactions in Female Cancer Development-a Population-Based Prospective Study. Hormones & cancer 9(4): 254-264

Hulley 1998

Hulley, S, Grady, D, Bush, T et al. (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 280(7): 605-13

Hulley 2002

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

Langer 2006

Langer, Robert D, Landgren, Britt Marie, Rymer, Janice et al. (2006) Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study. American journal of obstetrics and gynecology 195(5): 1320-7

Liang 2021

Liang, Ying, Jiao, Haoyan, Qu, Lingbo et al. (2021) Association Between Hormone Replacement Therapy and Development of Endometrial Cancer: Results From a Prospective US Cohort Study. Frontiers in medicine 8: 802959

Manson 2013

Manson, J.E., Chlebowski, R.T., Stefanick, M.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 2013 Oct 2;310(13):1353-68.

Mørch 2016

Mørch L, Kjaer S, Keiding N et al. (2016) The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. International Journal of Cancer 136(6): 1506-1515

Nachtigall 1979

Nachtigall, L E, Nachtigall, R H, Nachtigall, R D et al. (1979) Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstetrics and gynecology 54(1): 74-9

Obel 1993

Obel, E B, Munk-Jensen, N, Svenstrup, B et al. (1993) A two-year double-blind controlled study of the clinical effect of combined and sequential postmenopausal replacement therapy and steroid metabolism during treatment. Maturitas 16(1): 13-21

PEPI 1996

PEPI (1996) Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 275(5): 370-5

Prentice 2009

Prentice, Ross L, Manson, Joann E, Langer, Robert D et al. (2009) Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. American journal of epidemiology 170(1): 12-23

Prentice 2021

Prentice, Ross L, Aragaki, Aaron K, Chlebowski, Rowan T et al. (2021) Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone Therapy Among Women 50-59 Years of Age. American journal of epidemiology 190(3): 365-375

Rossouw 2022

Rossouw, Jacques E, Anderson, Garnet L, Prentice, Ross L et al. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288(3): 321-33

Schneider 2009

Schneider, C; Jick, S S; Meier, C R (2009) Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations. Climacteric: the journal of the International Menopause Society 12(6): 514-24

Sponholtz 2018

Sponholtz, Todd R, Palmer, Julie R, Rosenberg, Lynn A et al. (2018) Exogenous Hormone Use and Endometrial Cancer in U.S. Black Women. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 27(5): 558-565

Trabert 2013

Trabert, Britton, Wentzensen, Nicolas, Yang, Hannah P et al. (2013) Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? International journal of cancer 132(2): 417-26

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 endometrial cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362331
1.	Review title	Effects of hormone replacement therapy for menopausal symptoms on developing Endometrial cancer
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing endometrial cancer?
3.	Objective	To identify the effects, if any, of HRT on the risk of developing endometrial cancer
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 • HTA via CRD • INAHTA Searches will be restricted by: • English language

ID	Field	Content
		• Human studies • No date restriction The full search strategies will be published in the final review.
5.	Condition or domain being studied	Menopause
6.	Population	Women, non-binary and trans people with menopause (including perimenopause and post-menopause)

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 at the time it was prescribed 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
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• Incidence of endometrial cancer • Mortality from endometrial 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. Duplicate screening will not be undertaken for this question. 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:

ID	Field	Content
		• ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials ROBINS-I for non-randomised, controlled/cohort studies. The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** Mortality from endometrial cancer: 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.

ID	Field	Content

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

ID	Field	Content			
		group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	27th September 2022			
22.	Anticipated completion date	23rd August 2023			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☑
		Piloting of the study selection process		☐	☑
		Formal screening of search results against eligibility criteria		☐	☑
		Data extraction		☐	☑
		Risk of bias (quality) assessment		☐	☑
		Data analysis		☐	☑

ID	Field	Content
24.	Named contact	5a. Named contact Guideline development team NGA 5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
25.	Review team members	Senior Systematic Reviewer Systematic Reviewer
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362331
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

ID	Field	Content	
		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	Endometrial Neoplasms; Estrogen Replacement Therapy; Female; Humans; Menopause	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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

Appendix B Literature search strategies

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

There was a combined literature search strategies for review questions:

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

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

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

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

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

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

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

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

Clinical searches

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

Date of last search: 03/10/2022

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

#	Searches	
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	8328
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
14	or/6-13	300800
15	5 and 14	38439
16	exp Breast Neoplasms/	331829
17	exp "Neoplasms, Ductal, Lobular, and Medullary"/	45099
18	exp breast/ and exp neoplasms/	31705
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	412638
20	exp uterine neoplasms/	143954
21	Endometrial Hyperplasia/	3751
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	71639
23	exp Ovarian Neoplasms/	92941
24	Fallopian Tube Neoplasms/	3090
25	Peritoneal Neoplasms/	16848
26	Pelvic Neoplasms/	7356
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	134115
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	18696
29	exp Dementia/	195885
30	(amentia* or dementia* or lewy body).ti,ab.	131539
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	172723
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	212540
33	Death/ or exp Mortality/	438343
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	2676396
35	exp Cardiovascular Diseases/	2652417
36	exp Stroke/	164004
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	265024
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	391497
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	237740
40	(stroke or strokes).ti,ab.	293720
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	177232
42	TIA.ti,ab.	9584
43	(myocardial adj2 infarct*).ti,ab.	215115
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	85723
45	atrial flutter*.ti,ab.	6330
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	150990
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	23385
48	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/	98814
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	110885
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201

#	Searches	
52	exp Bone Remodeling/ or Bone Density/	118506
53	exp radius fractures/ or spinal fractures/ or hip fractures/	45889
54	(osteoporo* or osteop?en*).ti,ab.	91147
55	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	136427
56	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	76474
57	exp Muscle Strength/ or Muscle Contraction/ or Muscle, Skeletal/ or Muscle weakness/	275399
58	exp Muscular Atrophy/	20100
59	(sarcop?en* or dynap?eni*).ti,ab.	12753
60	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	89183
61	exp Diabetes Mellitus, Type 2/	162254
62	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	178683
63	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	3367
64	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1079
65	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	11970
66	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	52630
67	or/16-66	7071734
68	15 and 67	24780
69	animals/ not humans/	5018518
70	exp Animals, Laboratory/	944064
71	exp Animal Experimentation/	10221
72	exp Models, Animal/	633340
73	exp Rodentia/	3486788
74	(rat or rats or mouse or mice).ti.	1413148
75	or/69-74	6058843
76	68 not 75	22173
77	limit 76 to english language	19974
78	Climacteric/	4935
79	Menopause/ or Perimenopause/ or Postmenopause/	56226
80	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
81	("change of life" or life change?).ti,ab.	3175
82	or/78-81	117224
83	exp Hormone Replacement Therapy/	26181
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
86	exp *Estrogens/	97369
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
89	((combin* or sequen* or continu*) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	6337
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
91	or/83-90	300359
92	82 and 91	38419
93	animals/ not humans/	5018518
94	exp Animals, Laboratory/	944064
95	exp Animal Experimentation/	10221
96	exp Models, Animal/	633340
97	exp Rodentia/	3486788
98	(rat or rats or mouse or mice).ti.	1413148
99	or/93-98	6058843
100	92 not 99	34708

#	Searches	
101	limit 100 to english language	30818
102	randomized controlled trial.pt.	578276
103	controlled clinical trial.pt.	95066
104	pragmatic clinical trial.pt.	2153
105	randomi#ed.ab.	690521
106	placebo.ab.	232230
107	randomly.ab.	392671
108	Clinical Trials as topic.sh.	200427
109	trial.ti.	271569
110	or/102-109	1520899
111	COMPARATIVE STUDIES/	1911627
112	FOLLOW-UP STUDIES/	687669
113	TIME FACTORS/	1228326
114	reviewed.tw.	604810
115	prospective$.tw.	826138
116	retrospective$.tw.	951729
117	baseline.tw.	681295
118	cohort.tw.	716940
119	case series.tw.	96297
120	or/111-119	5840666
121	COHORT STUDIES/	319704
122	FOLLOW-UP STUDIES/	687669
123	LONGITUDINAL STUDIES/	160686
124	PROSPECTIVE STUDIES/	640096
125	RETROSPECTIVE STUDIES/	1062925
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	990520
127	(incidence? adj (stud* or research or analys*)).tw.	2167
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	8189
129	(prospective* adj method*).tw.	492
130	(retrospective* adj design*).tw.	2556
131	Case-Control Studies/	323880
132	"nested case control".ti,ab.	10276
133	or/121-132	2937576
134	110 or 120 or 133	7274173
135	101 and 134	16133
136	77 or 135	25292

Database: Embase <1974 to 2022 September 30>

Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
9	exp *estrogen/	126164
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068

#	Searches	
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
14	or/6-13	401114
15	5 and 14	58995
16	exp breast tumor/	610160
17	exp medullary carcinoma/	11738
18	exp breast/ and exp neoplasm/	81181
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	580028
20	exp uterus cancer/	178703
21	endometrium hyperplasia/	8475
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	94083
23	exp ovary tumor/	165879
24	uterine tube tumor/	1128
25	exp peritoneum tumor/	32297
26	exp pelvis tumor/	8687
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	189064
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	26375
29	exp dementia/	414481
30	(amentia* or dementia* or lewy body).ti,ab.	188972
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	233156
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	296024
33	death/ or fatality/ or exp mortality/	1565750
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	3638723
35	exp cardiovascular disease/	4653676
36	exp cerebrovascular accident/	278318
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	395575
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	582395
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	388936
40	(stroke or strokes).ti,ab.	467280
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	248980
42	TIA.ti,ab.	21167
43	(myocardial adj2 infarct*).ti,ab.	308381
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	151993
45	atrial flutter*.ti,ab.	10322
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	225615
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	38407
48	pulmonary embolism/ or lung embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or vein thrombosis/ or upper extremity deep vein thrombosis/	238572
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	173070
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963

#	Searches	
53	(osteoporo* or osteop?en*).ti,ab.	139235
54	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	184524
55	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	105447
56	muscle strength/ or muscle contraction/ or skeletal muscle/ or muscle weakness/	298183
57	exp muscle atrophy/	53010
58	(sarcop?en* or dynap?eni*).ti,ab.	19831
59	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	123477
60	diabetes mellitus/ or non insulin dependent diabetes mellitus/	903538
61	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	274466
62	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	4587
63	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1729
64	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	13941
65	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	87957
66	or/16-65	10247056
67	15 and 66	41567
68	animal/ not human/	1164743
69	nonhuman/	7043049
70	exp Animal Experiment/	2901019
71	exp Experimental Animal/	776639
72	animal model/	1589792
73	exp Rodent/	3873528
74	(rat or rats or mouse or mice).ti.	1563613
75	or/68-74	9201242
76	67 not 75	35048
77	limit 76 to english language	30447
78	climacterium/ or "menopause and climacterium"/	8994
79	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
80	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
81	("change of life" or life change?).tw.	4281
82	or/78-81	184584
83	exp hormone substitution/	61182
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
86	exp *estrogen/	126164
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
89	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
91	or/83-90	401114
92	82 and 91	58995
93	animal/ not human/	1164743
94	nonhuman/	7043049
95	exp Animal Experiment/	2901019
96	exp Experimental Animal/	776639
97	animal model/	1589792
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242

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

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

Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938
4	or/1-3	15066
5	hormone therapy/	2262
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *estrogens/	5657
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482

#	Searches	
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
11	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
12	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
13	or/5-12	24383
14	4 and 13	2373
15	breast neoplasms/	11017
16	Breast/ and exp neoplasms/	300
17	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	15213
18	uterus/ and exp neoplasms/	43
19	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	457
20	ovaries/ and exp neoplasms/	444
21	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	1347
22	((epithelial or germ cell) adj5 ovar*).ti,ab.	58
23	exp dementia/ or exp alzheimer's disease/	87977
24	(amentia* or dementia* or lewy body).ti,ab.	72463
25	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	67104
26	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	120339
27	exp "death and dying"/	45080
28	(death or dying or die* or dead or mortality or fatal*).ti,ab.	218375
29	exp Cardiovascular Disorders/ or Cerebrovascular Accidents/	68930
30	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	14620
31	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	16319
32	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	6390
33	(stroke or strokes).ti,ab,mh.	38668
34	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	14812
35	TIA.ti,ab.	993
36	(myocardial adj2 infarct*).ti,ab.	4538
37	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	1391
38	atrial flutter*.ti,ab.	27
39	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	4960
40	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).mp.	709
41	embolisms/ or thromboses/	1323
42	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	1179
43	osteoporosis/	1165
44	bones/ and (accidents/ or injuries/ or falls/)	117
45	(osteoporo* or osteop?en*).ti,ab.	2275
46	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab,mh.	2050
47	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab,mh.	1936
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357

#	Searches	
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *estrogens/	5657
73	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
75	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
76	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
77	or/69-76	24383
78	68 and 77	2373
79	animal.po.	432218
80	(rat or rats or mouse or mice).ti.	123700
81	79 or 80	436853
82	78 not 81	1974
83	limit 82 to english language	1898
84	clinical trial.md.	34832
85	clinical trial.md.	34832
86	Clinical trials/	12104
87	Randomized controlled trials/	913
88	Randomized clinical trials/	383
89	assign*.ti,ab.	106838
90	allocat*.ti,ab.	35101
91	crossover*.ti,ab.	8375
92	cross over*.ti,ab.	3251
93	((doubl* or singl*) adj blind*).ti,ab.	28070
94	factorial*.ti,ab.	21909
95	placebo*.ti,ab.	42984
96	random*.ti,ab.	229145
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0

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

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

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065

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

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

Date of last search: 03/10/2022

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

Database: Epistemonikos

Date of last search: 27/07/2022

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

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38

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

Database: INAHTA

Date of last search: 03/10/2022

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

Economic searches

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

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045

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

Database: Embase <1974 to 2022 July 27>

Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270

#	Searches	
8	letter.pt. or letter/	1241876
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

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

#	Searches	
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

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

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
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

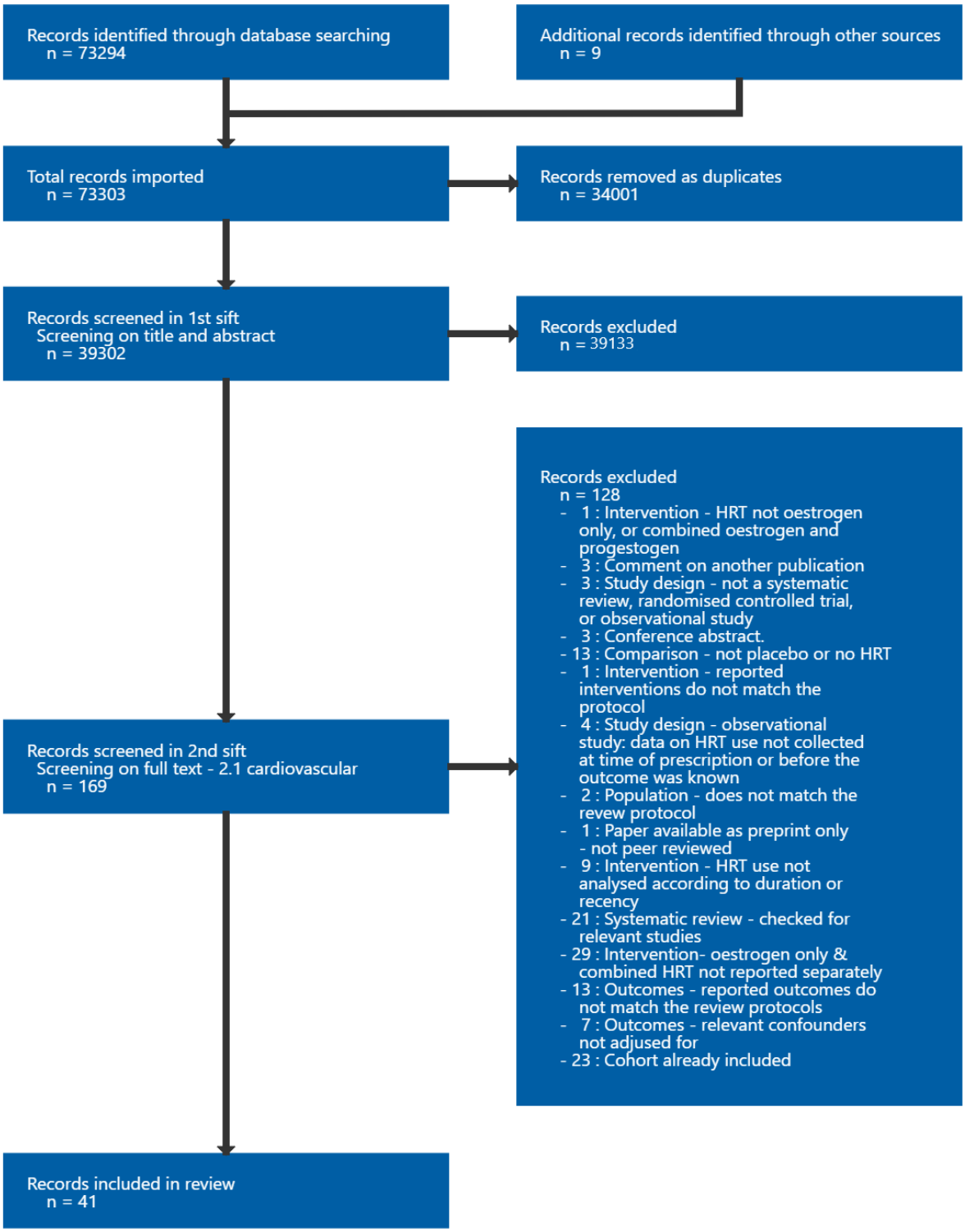
Date of last search: 28/07/2022

#	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 endometrial 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 endometrial cancer?

Table 4: Evidence tables

Allen, 2010

Bibliographic Reference	Allen, Naomi E; Tsilidis, Konstantinos K; Key, Timothy J; Dossus, Laure; Kaaks, Rudolf; Lund, Eiliv; Bakken, Kjersti; Gavrilyuk, Oxana; Overvad, Kim; Tjonneland, Anne; Olsen, Anja; Fournier, Agnes; Fabre, Alban; Clavel-Chapelon, Francoise; Chabbert-Buffet, Nathalie; Sacerdote, Carlotta; Krogh, Vittorio; Bendinelli, Benedetta; Tumino, Rosario; Panico, Salvatore; Bergmann, Manuela; Schuetze, Madlen; van Duijnhoven, Franzel J B; Bueno-de-Mesquita, H Bas; Onland-Moret, N Charlotte; van Gils, Carla H; Amiano, Pilar; Barricarte, Aurelio; Chirlaque, Maria-Dolores; Molina-Montes, Maria-Esther; Redondo, Maria-Luisa; Duell, Eric J; Khaw, Kay-Tee; Wareham, Nick; Rinaldi, Sabina; Fedirko, Veronika; Mouw, Traci; Michaud, Dominique S; Riboli, Elio; Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition.; American journal of epidemiology; 2010; vol. 172 (no. 12); 1394-403

Study details

Country/ies where study was carried out	Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom
Study type	Prospective cohort study
Study dates	1992-2000
Inclusion criteria	NR
Exclusion criteria	• women with prevalent cancer • hysterectomy • incomplete follow-up data • no baseline lifestyle questionnaire • premenopausal or perimenopausal at recruitment • never menstruated

	• missing data on both ever and current use of HRT • diagnosed with nonepithelial endometrial cancer
Patient characteristics	**Age (years) - mean±SD** • Never use: 58.7 (6.2) • Former use: 57.7 (5.1) • Current use: 54.6 (4.9) **BMI (kg/m2) - mean±SD** • Never use: 26.0 (4.6) • Former use: 25.1 (4.2) • Current use: 24.2 (3.7) **Ethnicity** Not reported **Age at menopause (years) - mean±SD** • Never use: 49.5 (4.3) • Former use: 49.5 (4.7) • Current use: 49.3 (4.7) **Age at last menstrual period (years) - mean±SD** Not reported **Previous use of HRT (ever used oral contraceptives) - %** • Never use: 37.1 • Former use: 50.5 • Current use: 62.7 **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: Oestrogen + progestogen HRT • Continuous

	• Sequential (progestin added usually 10-14 days of the month) Control: no HRT **Duration and recency of HRT use** Duration • Any duration of use • <2 years • >2 years Recency: • Current users
Duration of follow-up	10 years
Sources of funding	Not industry funded
Sample size	N=115474 women
Other information	Confounders: • adjusted for body mass index • parity • age at menopause • oral contraceptive use

Study arms

Oestrogen and progestogen HRT (N = 25000)

Oestrogen-only HRT (N = 4318)

No HRT (N = 64506)

Outcomes

Outcome	Oestrogen and progestogen HRT, N = 25000	Oestrogen-only HRT, N = 4318	No HRT, N = 64506

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(Low risk of bias due to confounding)*
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. For each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub-cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains

Section	Question	Answer
Overall bias	Directness	Directly applicable

Bakken, 2004

Bibliographic Reference	Bakken, Kjersti; Alsaker, Elin; Eggen, Anne Elise; Lund, Eiliv; Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study.; International journal of cancer; 2004; vol. 112 (no. 1); 130-4

Study details

Country/ies where study was carried out	Norway
Study type	Prospective cohort study
Study dates	1996 to 1998
Inclusion criteria	• women aged 45-64 years
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean** All population: 53 **BMI (kg/m2)- mean** All population: 25 **Ethnicity** Not reported **Age at menopause (years) - mean±SD** Not reported **Age at last menstrual period (years) - mean±SD** Not reported **Previous use of HRT** Not reported

	Hysterectomy before menopause Number of women aged 45-52 years and hysterectomy before menopause: 2039 **Family history of cancer** Not reported
Intervention(s)/control	Combined HRT (oestrogen-progestogen) • Sequential regimen • Continuous regimen **Duration and recency of HRT use** Oestrogen-only • No HRT Duration • Any duration of use Recency: • All users
Duration of follow-up	4 years
Sources of funding	Not industry funded
Sample size	N=67336 Endometrial cancer population: n=27,621
Other information	Confounders: • time since start of menopause • age at menarche • ever use of OCs • BMI • history of breast cancer in mother • regions with a screening program • age at first birth • parity

Study arms

Oestrogen and progestogen HRT (N = 7268)

Oestrogen-only HRT (N = 1123)

Oestrogen-only and estriol combined

No HRT (N = 16035)

Outcomes

Outcome	Oestrogen and progestogen HRT, N = 7268	Oestrogen-only HRT, N = 1123	No HRT, N = 16035

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome)*
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(The analysis is unlikely to have removed the risk of bias arising from the missing data.)*

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(The methods of outcome assessment were comparable across intervention groups and the outcome measure is only minimally influenced by knowledge of the intervention received by study participants. Any error in measuring the outcome is only minimally related to intervention status.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low or moderate risk of bias for all domains.
Overall bias	Directness	Directly applicable

Beral, 2005

Bibliographic Reference	Beral, Valerie; Bull, Diana; Reeves, Gillian; Million Women Study, Collaborators; Endometrial cancer and hormone-replacement therapy in the Million Women Study.; Lancet (London, England); 2005; vol. 365 (no. 9470); 1543-51

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	1996 to 2001
Inclusion criteria	• women without a hysterectomy
Exclusion criteria	• any type of cancer registered before recruitment, except nonmelanoma skin cancer

Patient characteristics	**Age (years)- mean±SD** Oestrogen and progestogen: 57 (3.6) Oestrogen-only: 57.1 (4.1) No HRT: 58 (4.3) **BMI (kg/m2)- mean±SD** Oestrogen and progestogen: 25.5 (4.2) Oestrogen-only: 25.6 (4.3) No HRT: 26.3 (4.8) **Ethnicity** Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (oral contraceptives)- n (%)** Oestrogen and progestogen: 44472 (64) Oestrogen-only: 8605 (62) No HRT: 182800 (47) **Hysterectomy before menopause** N/A (women with hysterectomy excluded) **Family history of cancer** Not reported
Intervention(s)/control	Oestrogen + progestogen (continuous) HRT Oestrogen-only HRT No HRT **Duration and recency of HRT use** Duration • Any duration of use

	• <5 years • ≥5 years Recency: • All users
Duration of follow-up	3.4 years
Sources of funding	Not industry funded
Sample size	N=716738 Oestrogen and progestogen: n=215100 Oestrogen-only: 14200 No HRT: 395800
Other information	Confounders: • time since menopause • parity • oral contraceptive use • body-mass index • alcohol consumption • region of residence • socioeconomic status

Study arms

Oestrogen and progestogen HRT (N = 215100)

Oestrogen-only HRT (N = 14200)

No HRT (N = 395800)

Outcomes

Outcome	Oestrogen and progestogen HRT, N = 215100	Oestrogen-only HRT, N = 14200	No HRT, N = 395800

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome)*
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(The analysis is unlikely to have removed the risk of bias arising from the missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(The methods of outcome assessment were comparable across intervention groups and the outcome measure is only minimally influenced by knowledge of the intervention received by study participants. Any error in measuring the outcome is only minimally related to intervention status)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low or moderate risk of bias for all domains.

Section	Question	Answer
Overall bias	Directness	Directly applicable

Byrjalsen, 1999

Bibliographic Reference	Byrjalsen, I; Bjarnason, N H; Christiansen, C; Progestational effects of combinations of gestodene on the postmenopausal endometrium during hormone replacement therapy.; American journal of obstetrics and gynaecology; 1999; vol. 180 (no. 3pt1); 539-49

Study details

Country/ies where study was carried out	Denmark
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• healthy postmenopausal women aged 45 to 63 years
Exclusion criteria	• diseases or medications known to influence the study measurements
Patient characteristics	**Age (years) - mean±SD** Overall mean age: 53.4 years, SD: NR Sequential 2 mg, estradiol, 50 mg gestodene: 53.5 (2.8) Sequential 2 mg, estradiol, 25 mg gestodene: 53.3 (29) Sequential 1 mg, estradiol, 25 mg gestodene: 53.2 (2.7) Continuous 1 mg, estradiol, 25 mg gestodene: 53.6 (3.2) Placebo: 53.7 (3.0) **BMI (kg/m2)- mean±SD** Not reported **Ethnicity** Not reported **Age at menopause (years)- mean±SD**

	Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • Sequential 2 mg, estradiol, 50 µg gestodene on days 17 to 28 • Sequential 2 mg, estradiol, 25 µg gestodene on days 17 to 28 • Sequential 1 mg, estradiol, 25 µg gestodene on days 17 to 28 • Continuous 1 mg, estradiol, 25 µg gestodene Placebo **Duration and recency of HRT use** Duration • 2 years Recency: • Current users
Duration of follow-up	2 years
Sources of funding	Not industry funded
Sample size	N=278 Oestrogen and progestogen HRT (sequential, 2mg, 50mg respectively): n=30 Oestrogen and progestogen HRT (sequential, 2mg, 25mg respectively): n=27 Oestrogen and progestogen HRT (sequential, 1mg, 25mg respectively): n=34 Oestrogen and progestogen HRT (continuous, 1mg, 25mg respectively): n=34 Placebo: n=43

Study arms

Oestrogen and progestogen HRT (sequential, 2mg, 50mg respectively) (N = 30)

Oestrogen and progestogen HRT (sequential, 2mg, 25mg respectively) (N = 27)

Oestrogen and progestogen HRT (sequential, 1mg, 25mg respectively) (N = 34)

Oestrogen and progestogen HRT (continuous, 1mg, 25mg respectively) (N = 34)

Placebo (N = 43)

Outcomes

Outcome	Oestrogen and progestogen HRT (sequential, 2mg, 50mg respectively), N = 30	Oestrogen and progestogen HRT (sequential, 2mg, 25mg respectively), N = 27	Oestrogen and progestogen HRT (sequential, 1mg, 25mg respectively), N = 34	Oestrogen and progestogen HRT (continuous, 1mg, 25mg respectively), N = 34	Placebo, N = 43

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(There is no information about concealment of the allocation sequence and randomised, however any baseline differences observed between intervention groups appear to be compatible with chance.)*
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)	Some concerns *(Participants, carers and people delivering the interventions were likely unaware of intervention groups during the trial however there is no information on whether there were deviations from intended intervention because of the trial context. It appears than an appropriate analysis was not used to estimate the effect of assignment to intervention however the potential impact (on the estimated effect of intervention) of the failure to*

Section	Question	Answer
		analyse participants in the group to which they were randomized was not substantial)
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)	High *(Participants, carers and people delivering the interventions were likely unaware of intervention groups during the trial however failures in implementing the intervention could have affected the outcome. It appears that an appropriate analysis was not used to estimate the effect of adhering to intervention.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Outcome data were not available for all, or nearly all, randomized participants. There is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value and it is likely that missingness in the outcome depended on its true value (One fourth of the women in the 2 groups receiving 2 mg oestradiol discontinued the study because of uterine bleeding, as opposed to an eighth in the 2 groups of women receiving only 1 mg oestradiol. Rates of discontinuation because of other adverse effects from the study medication were comparable in all 4 hormone groups at approximately 15%).)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(There is no information on whether the result being assessed is likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and from multiple eligible analyses of the data, however this is unlikely.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	High *(The study has a high risk of bias due to deviations from the intended interventions (effect of adhering to intervention), missing outcome data, and some concerns due to the randomisation process, deviations from the intended interventions (effect of assignment to intervention) and selection of the reported result.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Cherry, 2002

Bibliographic Reference Cherry, Nicola; Gilmour, Kyle; Hannaford, Philip; Heagerty, Anthony; Khan, Mohammed Amjed; Kitchener, Henry; McNamee, Roseanne; Elstein, Max; Kay, Clifford; Seif, Mourad; Buckley, Hilary; ESPRIT, team; Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo-controlled trial.; Lancet (London, England); 2002; vol. 360 (no. 9350); 2001-8

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	1996 to 2000
Inclusion criteria	• 50–69 years • meet diagnostic criteria for myocardial infarction • discharged alive from hospital within 31 days of admission • no previous documented myocardial infarction • no other exclusion condition.

Exclusion criteria	• use of HRT or vaginal bleeding in the 12 months before admission • history of breast, ovarian, or endometrial carcinoma • active thrombophlebitis • history of deep-vein thrombosis or pulmonary embolism • acute or chronic liver disease • Rotor syndrome • Dubin-Johnson syndrome • severe renal disease
Patient characteristics	**Age (years) - mean±SD (age at admission to hospital)** Oestrogen-only (Oestradiol valerate): 62.3 (5.2) Placebo: 62.9 (4.9) Overall mean age: 62.6 **BMI (kg/m2) - mean±SD** Oestrogen-only (Oestradiol valerate): 26.8 (5.1) Placebo: 26.7 (5.3) **Ethnicity (white) - n (%)** Oestrogen-only (Oestradiol valerate): 496 (97) Placebo: 489 (97) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Oestrogen-only (Oestradiol valerate): 46.3 (5.8) Placebo: 46.6 (5.7) **Previous use of HRT (>12 months before admission)- n (%)** Oestrogen-only (Oestradiol valerate): 62 (12) Placebo: 51 (10) **Hysterectomy before menopause- n (%)** Oestrogen-only (Oestradiol valerate): 140 (27)

	Placebo: 105 (21) **Family history of cancer** Not reported
Intervention(s)/control	Oestrogen-only Oestradiol valerate 2mg taken orally Placebo placebo pill taken orally **Duration and recency of HRT use** Duration • 2 years Recency: • Current users
Duration of follow-up	3, 6, 12, and 18 months after study entry and at 24 months after finishing treatment
Sources of funding	The work was funded by the UK National Health Service Research and Development Programme on Cardiovascular Disease and Stroke, which provided funding for recruitment and the initial phases of follow-up. Follow-up was completed with funds from the University of Manchester, with additional input from Schering Health Care Limited. Schering AG also funded KG during the final 3 years of the project
Sample size	N=1,017

Study arms

Oestrogen-only HRT (N = 513)

Placebo (N = 504)

Outcomes

Outcome	Oestrogen-only HRT, N = 513	Placebo, N = 504

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (the trial statistician used a restricted randomisation scheme based on a block size of four to generate a list of treatment allocations) and any baseline differences observed between intervention groups appear to be compatible with chance)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate analysis (intention to treat) was used to estimate the effect of assignment to intervention)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and study participants adhered to the assigned intervention regimen)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants (no losses to follow-up))*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome*

Section	Question	Answer
		data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Cherry, 2014

Bibliographic Reference	Cherry, N; McNamee, R; Heagerty, A; Kitchener, H; Hannaford, P; Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial.; BJOG : an international journal of obstetrics and gynaecology; 2014; vol. 121 (no. 6); 700-705

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	1996 to 2000
Inclusion criteria	• women age 50-69 years who had survived a first MI
Exclusion criteria	• history of cancer or use of hormone replacement therapy in the previous 12 months
Patient characteristics	**Age (years)- mean±SD** Not reported **BMI (kg/m2)- mean±SD** Not reported **Ethnicity**

	Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: estradiol valerate 2mg Placebo **Duration and recency of HRT use** Duration • 2 years Recency: • Past users of 12.6 years (mean)
Duration of follow-up	2 years of HRT in ESPRIT trial, follow-up at 14 years
Sources of funding	Not industry funded
Sample size	N=1017 Intervention: n=513 Placebo: n=504

Study arms

Oestrogen-only HRT (N = 513)

Placebo (N = 504)

Outcomes

Outcome	Oestrogen-only HRT, N = 513	Placebo, N = 504

Outcomes: Incidence of endometrial cancer, Mortality of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (the trial statistician used a restricted randomisation scheme based on a block size of four to generate a list of treatment allocations) and any baseline differences observed between intervention groups appear to be compatible with chance)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate analysis (intention to treat) was used to estimate the effect of assignment to intervention)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and study participants adhered to the assigned intervention regimen)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was*

Section	Question	Answer
		finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Chlebowski, 2016

Bibliographic Reference Chlebowski, R T; Anderson, G L; Sarto, G E; Haque, R; Runowicz, C D; Aragaki, A K; Thomson, C A; Howard, B V; Wactawski-Wende, J; Chen, C; Rohan, T E; Simon, M S; Reed, S D; Manson, J E; Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial.; Journal of the National Cancer Institute; 2016; vol. 108 (no. 3)

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• postmenopausal women aged 50 to 79 years with an intact uterus
Exclusion criteria	• prior breast cancer

	• anticipated survival of less than 3 years • previous invasive cancer within 10 years
Patient characteristics	**Age (years)- n (%)** Oestrogen + progestogen: • 50-54: 846 (12.9) • 55-59: 1420 (21.7) • 60-69: 3019 (46.1) • 70-79: 1260 (19.3) Placebo: • 50-54: 767 (12.3) • 55-59: 1361 (21.8) • 60-69: 2887 (46.2) • 70-79: 1228 (19.7) **BMI (kg/m2)- n (%)** Oestrogen + progestogen: • <25: 1998 (30.7) • 25-<30: 2278 (35.0) • 30-<35: 1396 (21.4) • 35-<40: 593 (9.1) • ≥40: 251 (3.9) Placebo: • <25: 1949 (31.4) • 25-<30: 2215 (35.7) • 30-<35: 1250 (20.2) • 35-<40: 523 (8.4) • ≥40: 265 (4.3) **Ethnicity- n (%)** Oestrogen + progestogen: • White: 5616 (85.8)

	• Black: 406 (6.2) • Hispanic: 291 (4.4) • American Indian: 16 (0.2) • Asian/Pacific Islander: 132 (2.0) • Unknown: 84 (1.3) Placebo: • White: 5357 (85.8) • Black: 401 (6.4) • Hispanic: 261 (4.2) • American Indian: 14 (0.2) • Asian/Pacific Islander: 128 (2.1) • Unknown: 84 (1.3) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n (%)** Oestrogen + progestogen: • Unopposed oestrogen use ever: 682 (10.4) • Oestrogen + progesterone use ever: 1215 (18.6) Placebo: • Unopposed oestrogen use ever: 645 (10.3) • Oestrogen + progesterone use ever: 1131 (18.1) **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: 0.625 mg/day CEE plus 2.5 mg/day MPA Placebo

Duration of follow-up	13 years median cumulative follow-up, 5.6 years intervention
Sources of funding	Not industry funded
Sample size	N=16608 Intervention: n=6545 Control: n=6243

Study arms

Oestrogen + progestogen HRT (N = 6545)

Placebo (N = 6243)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 6545	Placebo, N = 6243

Outcomes: Incidence of endometrial cancer, incidence of mortality from endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computerized, permuted-block algorithm and a secured database system were implemented by the WHI Clinical Coordinating Centre for drug dispensing) and any baseline differences observed between intervention groups appear to be compatible with chance,)*
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 *(Most participants, carers and people delivering the interventions were unaware of intervention groups during the trial (when initiated in 1993, the trial originally included random assignment to an oestrogen alone arm, however clinical trial results indicated oestrogen alone increased endometrial epithelial proliferation and so, that arm was dropped and the 331 women in the oestrogen alone group were added to the combined therapy group which*

Section	Question	Answer
		broke the blinding for that group). An appropriate (intention to treat) analysis was used to estimate the effect of assignment to intervention.)
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 *(Most participants, carers and people delivering the interventions were unaware of intervention groups during the trial. There were failures in implementing the intervention (331 participants who stopped oestrogen-only were reassigned to the combined hormone replace therapy) however this was 3.9% of participants included and was unlikely to affect the outcome.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Ferenczy, 2002

Bibliographic Reference	Ferenczy, A; Gelfand, M M; van de Weijer, P H M; Rioux, J E; Endometrial safety and bleeding patterns during a 2-year study of 1 or 2 mg 17 beta-estradiol combined with sequential 5-20 mg dydrogesterone.; Climacteric : the journal of the International Menopause Society; 2002; vol. 5 (no. 1); 26-35

Study details

Country/ies where study was carried out	Canada
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• nonhysterectomized, postmenopausal women aged 45–65 years • naturally or surgically postmenopausal • serum follicle stimulating hormone (FSH) levels within the normal postmenopausal range
Exclusion criteria	• presence of abnormal (uninvestigated) vaginal bleeding in the previous 6 months • the use of oestrogens and/or progestogens and/or androgens in the preceding 6 months • previous unopposed oestrogen therapy for 6 months or more • any previous use of estradiol pellet/implant therapy
Patient characteristics	**Age (years)- mean±SD** Mean age: 55.6, SD: NR Placebo: 56.4 (4.7) 1/5 mg: 55.1 (4.7) 1/10 mg: 55.4 (4.5) 2/10 mg: 56 (4.8) 2/20 mg: 55.1 (4.5) **BMI (kg/m2)- mean±SD** Not reported **Ethnicity**

	Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • 1 mg/day 17b-estradiol sequentially combined with 5 (1/5) or 10 mg/day dydrogesterone (1/10) for the last 14 days of each 28-day cycle • 2 mg/day 17b-estradiol sequentially combined with 10 (2/10) or 20 mg/day dydrogesterone (2/20) for the last 14 days of each 28-day cycle Control: • oral treatment with tablets containing placebo
Duration of follow-up	2 years
Sources of funding	Industry funded (Solvay Pharmaceuticals)
Sample size	N=579 Placebo: n = 113 1/5 mg: n = 117 1/10 mg: n = 114 2/10 mg: n = 117 2/20 mg: n = 118

Study arms

Oestrogen + progestogen HRT (1/5mg) (N = 117)

Oestrogen + progestogen HRT (1/10mg) (N = 114)

Oestrogen + progestogen HRT (2/10mg) (N = 117)

Oestrogen + progestogen HRT (2/20mg) (N = 118)

Placebo (N = 113)

Outcomes

Outcome	Oestrogen + progestogen HRT (1/5mg), N = 117	Oestrogen + progestogen HRT (1/10mg), N = 114	Oestrogen + progestogen HRT (2/10mg), N = 117	Oestrogen + progestogen HRT (2/20mg), N = 118	Placebo, N = 113

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(There is no information about concealment of the allocation sequence and randomisation, however any baseline differences observed between intervention groups appear to be compatible with chance.)*
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)	Some concerns *(The study is described as double blind, so it is likely that participants, carers and people delivering the interventions were unaware of intervention groups during the trial however this is unclear and there is no information on whether there were deviations from intended intervention because of the trial context. It appears than an appropriate analysis was not used to estimate the effect of assignment to intervention however the potential impact (on the estimated effect of intervention) of the failure to analyse participants in the group to which they were randomized was not substantial,)*
Domain 2b: Risk of bias due to deviations from the intended	Risk of bias judgement for deviations from the intended	High *(Participants, carers and people delivering the interventions were likely*

Section	Question	Answer
interventions (effect of adhering to intervention)	interventions (effect of adhering to intervention)	*unaware of intervention groups during the trial however failures in implementing the intervention could have affected the outcome. It appears that an appropriate analysis was not used to estimate the effect of adhering to intervention.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Outcome data were not available for all, or nearly all, randomized participants. There is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value and it is likely that missingness in the outcome depended on its true value (biopsies were not available for137 women from the all-patient sample, mainly because they remained on treatment for less than 1 year, or they were receiving placebo and therefore did not require a biopsy if they withdrew prematurely from the study at any time).)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the assessment of the outcome is likely not to have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	High *(The study is at high risk of bias due to deviations from the intended interventions (effect of adhering to intervention), missing outcome data and*

Section	Question	Answer
		some concerns due to the randomisation process and deviations from the intended interventions (effect of assignment to intervention).)
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Fournier, 2014

Bibliographic Reference	Fournier, Agnes; Dossus, Laure; Mesrine, Sylvie; Vilier, Alice; Boutron-Ruault, Marie-Christine; Clavel-Chapelon, Francoise; Chabbert-Buffet, Nathalie; Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008.; American journal of epidemiology; 2014; vol. 180 (no. 5); 508-17

Study details

Country/ies where study was carried out	France
Study type	Prospective cohort study
Study dates	1992 to 2008
Inclusion criteria	• women aged 40–65 years • residing in continental France • insured by a national health insurance fund that mainly covers teachers and their family
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean±SD** Overall age at diagnosis: 64.3 (6.5) **BMI (kg/m2)- n (%)** ≤20: 8,945 (13.6) 20.1–24.9: 41,785 (63.7)

	25–29.9: 11,963 (18.2) ≥30: 2,937 (4.5) **Ethnicity** Not reported **Age at menopause (years)- n (%)** <48: 9,160 (14.0) 48–51: 31,004 (47.2) ≥52: 25,466 (38.8) **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (progestogen alone)- n (%)** Never: 38308 (58.4) Ever: 27322 (41.6) **Hysterectomy before menopause** Not reported **Family history of cancer (endometrial cancer in first-degree relatives)- n (%)** No: 50615 (77.1) Yes: 15015 (22.9)
Intervention(s)/control	Intervention: • oestrogen plus micronised progesterone HRT • oestrogen-only HRT Control: • no HRT
Duration of follow-up	Mean follow up: 10.8 years
Sources of funding	Not industry funded
Sample size	N=65630

Other information	Confounders: • age • age at menopause • parity • use of oral contraceptives • premenopausal use of progesterone alone • recent gynaecological exam • history of diabetes • history of high blood pressure

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen-only HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen-only HRT, N = NR	No HRT, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected)*
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 for each participant, start of follow up and start of intervention coincided.)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Gambrell Jr., 1979

Bibliographic Reference Gambrell Jr., R.D.; Massey, F.M.; Castaneda, T.A.; Ugenas, A.J.; Ricci, C.A.; Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens; Journal of the American Geriatrics Society; 1979; vol. 27 (no. 9); 389-394

Study details

Country/ies where study was carried out	US
Study type	Retrospective cohort study
Study dates	1975 to 1977
Inclusion criteria	• postmenopausal (evidenced either by one-year cessation of menses) • administration of oestrogen replacement therapy for at least one year
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean** 57.3 **BMI (kg/m2)- mean±SD** Not reported **Ethnicity** Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • oestrogen and progestogen HRT • oestrogen-only HRT

	Control: • no HRT
Duration of follow-up	3 years
Sources of funding	Not industry funded
Sample size	Not reported
Other information	No confounders reported

Outcomes

Outcome	Study, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Heiss, 2008

Bibliographic Reference	Heiss, G.; Wallace, R.; Anderson, G.L.; Aragaki, A.; Beresford, S.A.A.; Brzyski, R.; Chlebowski, R.T.; Gass, M.; LaCroix, A.; Manson, J.E.; Prentice, R.L.; Rossouw, J.; Stefanick, M.L.; Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin; JAMA; 2008; vol. 299 (no. 9); 1036-1045

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	2002 to 2005
Inclusion criteria	• postmenopausal women aged 50 through 79 years • with an intact uterus

	• written informed consent
Exclusion criteria	Not reported
Patient characteristics	**Age (years), mean±SD** Mean age: 63.2, SD: NR Oestrogen + progestogen HRT: 63.1 (7.1) Placebo: 63.3 (7.1) **BMI (kg/m2), n (%)** Oestrogen + progestogen HRT: • <25: 2430 (30.3) 2373 (31.1) • 25-<30: 2826 (35.3) 2689 (35.2) .48 • ≥30: 2760 (34.4) 2568 (33.7) Placebo: • <25: 2373 (31.1) • 25-<30: 2689 (35.2) .48 • ≥30: 2568 (33.7) **Ethnicity, n (%)** Oestrogen + progestogen HRT: • White: 6788 (84.3) • Black: 517 (6.4) • Hispanic: 426 (5.3) • American Indian: 24 (0.3) • Asian/Pacific Islander: 180 (2.2) • Unknown: 117 (1.5) Placebo: • White: 6477 (84.4) • Black: 533 (6.9) • Hispanic: 385 (5.0) .56 • American Indian: 27 (0.4)

	• Asian/Pacific Islander: 156 (2.0) • Unknown: 100 (1.3) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (past user)- n (%)** Oestrogen + progestogen HRT: 1589 (19.7) Placebo: 1492 (19.4) **Hysterectomy before menopause** N/A (women with hysterectomy excluded) **Family history of cancer (breast cancer, female)- n (%)** Oestrogen + progestogen HRT: 1213 (15.9) Placebo: 1110 (15.3)
Intervention(s)/control	Intervention: 0.625 mg/day CEE plus 2.5 mg/day MPA Control: placebo
Duration of follow-up	Mean follow up: 2.4 years
Sources of funding	Not industry funded
Sample size	N=16608 Oestrogen + progestogen HRT: n=8052 Placebo: 7678

Study arms

Oestrogen + progestogen HRT (N = 8052)

Placebo (N = 7678)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 8052	Placebo, N = 7678

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate (intention to treat) analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results,*

Section	Question	Answer
		from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Holm, 2018

Bibliographic Reference	Holm, Marianne; Olsen, Anja; Kyro, Cecilie; Overvad, Kim; Kroman, Niels; Tjonneland, Anne; The Influence of Menopausal Hormone Therapy and Potential Lifestyle Interactions in Female Cancer Development-a Population-Based Prospective Study.; Hormones & cancer; 2018; vol. 9 (no. 4); 254-264

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	1993 to 1997
Inclusion criteria	• women aged 50–64 • born in Denmark • without a previous cancer diagnosis
Exclusion criteria	Not reported
Patient characteristics	**Age at baseline (years)- median (5, 95%)** 56 (50 to 54)

	BMI (kg/m2)- n (%) • Underweight <18.5: 368 (1.3) • Normal 18.5–24.99: 14,451 (49.6) • Overweight 25–29.99: 10,169 (34.9) **Ethnicity** Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (use of oral contraceptives ever)** Yes: 16854 (57.8) No: 12082 (41.4) **Hysterectomy before menopause** Not reported **Family history of cancer** Yes: 12378 (42.5) No: 13099 (44.9)
Intervention(s)/control	Intervention: • oestrogen plus progestogen • oestrogen-only Control: • no HRT
Duration of follow-up	Median follow up: 15.9 years
Sources of funding	Not industry funded
Sample size	N=29,152
Other information	Confounders:

	• age • age at menarche • parity • age at first childbirth • history of oral contraceptive pill use • adult attained height • education level • baseline alcohol intake • BMI • physical activity • smoking • diet

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen-only HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen-only HRT, N = NR	No HRT, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*

Section	Question	Answer
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub cohorts)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Hulley, 1998

Bibliographic Reference	Hulley, S; Grady, D; Bush, T; Furberg, C; Herrington, D; Riggs, B; Vittinghoff, E; Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.; JAMA; 1998; vol. 280 (no. 7); 605-13

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	Postmenopausal women aged <80 years with established coronary disease who had not had a hysterectomy. Postmenopausal was defined as age ≥55 years and no natural menses for at least 5 years or no natural menses or at least 1 year and serum follicle stimulating hormone (FSH) level more than 40IU/L, or documented bilateral oophorectomy with FSH level more than 40 IU/L and estradiol level less than 92pmol/L (25pg/mL). Established coronary disease was defined as evidence of 1 or more of the following: MI, coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries
Exclusion criteria	CHD event within 6 months of randomization; serum triglyeride level higher than 3.39 mmol/L (300mg/dL); use of oral, parenteral, vaginal or transdermal sex hormones within 3 months of the screening visit; history of deep vein thrombosis of pulmonary embolism; history of breast cancer or breast examination or mammogram suggestive of breast cancer; history of endometrial cancer,; abnormal uterine bleeding, endometrial hyperplasia, or endometrium thickness greater than 5mm on baseline evaluation; abnormal or unobtainable papanicolaou test result; serum aspartate aminotransferese level more than 1.2 times normal; unlikely to remain geographically accessible for study visits for at least 4 years; disease (other than CHD) judged likely to be fatal within 4 years; New York Heart association class IV or severe class III congestive heart failure; alcoholism or other drug abuse; uncontrolled hypertension (diastolic blood pressure ≥105 mm Hg or systolic blood pressure ≥200 mm Hg); uncontrolled diabetes fasting blood glucose level ≥16.7 mmol/L (300 mg/dL); participation in another investigational drug or device study; less than 80% compliance with a placebo run-in prior to randomization; or history of intolerance to hormone therapy,
Patient characteristics	**Age (years)- mean±SD** Mean age: 66.7, SD: NR

	CEE plus MPA: 67 (7) Placebo: 67 (7) **BMI (kg/m2)- >27, %** CEE plus MPA: 57 Placebo: 55 **Ethnicity, white- %** CEE plus MPA: 88 Placebo: 90 **Age at menopause (years)- mean±SD** Not reported **Time since last menstrual period (years)- mean±SD** CEE plus MPA: 18 (8) Placebo: 18 (8) **Previous use of HRT (postmenopausal oestrogen use)- n** CEE plus MPA: 24 Placebo: 23 **Hysterectomy before menopause** N/A (women with hysterectomy excluded) **Family history of cancer** Not reported
Intervention(s)/control	CEE plus MPA 1 tablet daily containing both conjugated equine oestrogens, 0.625mg and medroxyprogesterone acetate, 2.5 mg (oestrogen plus progestin), Prempro Placebo 1 placebo tablet of identical appearance
Duration of follow-up	Follow-up every 4 months with a mean follow-up of 4.75 years
Sources of funding	Sponsored by Wyeth-Ayerst Research, Radnor

Sample size	N=2763

Study arms

Oestrogen + progestogen HRT (N = 1380)

Placebo (N = 1383)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 1380	Placebo, N = 1383

Outcome: Incidence of endometrial cancer. See Appendix L for details on data

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and study participants adhered to the assigned intervention regimen)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hulley, 2002

Bibliographic Reference Hulley, Stephen; Furberg, Curt; Barrett-Connor, Elizabeth; Cauley, Jane; Grady, Deborah; Haskell, William; Knopp, Robert; Lowery, Maureen; Satterfield, Suzanne; Schrott, Helmut; Vittinghoff, Eric; Hunninghake, Donald; HERS Research, Group; Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).; JAMA; 2002; vol. 288 (no. 1); 58-66

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)

Study dates	1993 to 2000
Inclusion criteria	Postmenopausal women aged <80 years with established coronary disease who had not had a hysterectomy.
Exclusion criteria	history of deep vein thrombosis or pulmonary embolism, history of breast cancer, endometrial hyperplasia or caner, abnormal papanicolaou (pap) result, any hormone use within the past 3 months, and disease judged likely to be fatal within 4 years
Patient characteristics	**Age (years)- mean±SD** Mean age: 66.7, SD: NR **HERS** CEE plus MPA: 67 (7) Placebo: 67 (7) **HERS II** CEE plus MPA: 67 (7) Placebo: 67 (7) **BMI (kg/m2)- mean±SD** **HERS** CEE plus MPA: 29 (6) Placebo: 29 (6) **HERS II** CEE plus MPA: 29 (5) Placebo: 29 (5) **Ethnicity, White- %** **HERS** CEE plus MPA: 88 Placebo: 90 **HERS II** CEE plus MPA: 89 Placebo: 91 **Age at menopause (years)- mean±SD**

	Not reported **Age at last menstrual period (years)- mean±SD** **HERS** CEE plus MPA: 49 (5) Placebo: 49 (5) **HERS II** CEE plus MPA: 49 (5) Placebo: 49 (5) **Previous use of HRT (past use of oestrogens)- %** **HERS** CEE plus MPA: 24 Placebo: 23 **HERS II** CEE plus MPA: 25 Placebo: 23 **Hysterectomy before menopause** N/A (women with hysterectomy excluded) **Family history of cancer (breast cancer)- %** **HERS** CEE plus MPA: 12 Placebo: 11 **HERS II** CEE plus MPA: 12 Placebo: 12
Intervention(s)/control	CEE plus MPA 0.625 mg/d of conjugated oestrogens plus 2.5 mg of medroxyprogesterone acetate Placebo Identical placebo

Duration of follow-up	4.1 years duration (HERS) and subsequent open-label observational follow-up for 2.7 years (HERS II)
Sources of funding	Wyeth-Ayerst Research funded the study
Sample size	N=2763

Study arms

Oestrogen + progestogen HRT (N = 1380)

Placebo (N = 1383)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 1380	Placebo, N = 1383

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and study participants adhered to the assigned intervention regimen)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Langer, 2006

Bibliographic Reference	Langer, Robert D; Landgren, Britt Marie; Rymer, Janice; Helmond, Frans A; OPAL, Investigators; Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study.; American journal of obstetrics and gynaecology; 2006; vol. 195 (no. 5); 1320-7

Study details

Country/ies where study was carried out	US and Europe

Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• healthy postmenopausal women • 45-79 years • body mass index of >19 and ≤32 kg/m2) • amenorrheic for ≥1 year
Exclusion criteria	• abnormal cervical Pap smear result • double-layer endometrial thickness • endometrial hyperplasia • unexplained vaginal bleeding • uncontrolled hypertension • current or recent alcohol and/or drug abuse • Type I diabetes mellitus • low total fasting cholesterol • recent history of myocardial infarction • heart failure requiring pharmacologic treatment • current or previous stroke • thrombophlebitis • thromboembolic disorder • gallbladder disease • malignancy (except nonmelanoma skin cancer) • suspected breast malignancy • relevant abnormal electrocardiogram (ECG) or laboratory values • serious decompensated renal or liver disease • a carotid ultrasound alert • carotid arteries that were difficult to image using the study protocol • any condition that could alter the pharmacokinetics of the investigational drugs • hypersensitivity to tibolone or CEE/MPA

Patient characteristics	**Age (years)- mean±SD** Mean age: 58.6, SD: NR CEE/MPA: 58.7 (6.6) Placebo: 58.6 (6.6) **BMI (kg/m2)- mean±SD** CEE/MPA: 25.3 (3.0) Placebo: 24.9 (2.9) **Ethnicity- n (%)** CEE/MPA: • Caucasian: 275 (96.8) • Asian: 5 (1.7) • Other: 4 (1.4) Placebo: • Caucasian: 274 (95.4) • Asian: 7 (2.4) • Other: 6 (2.0) **Mean time since menopause (years)- mean±SD** CEE/MPA: 10.6 (7.6) Placebo: 10.8 (7.8) **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n (%)** CEE/MPA: 142 (50) Placebo: 131 (45.6) **Hysterectomy before menopause (intact uterus)- n (%)** CEE/MPA: 236 (83) Placebo: 243 (84.6) **Family history of cancer** Not reported

Intervention(s)/control	Intervention: • 0.625 mg/day CEE plus 2.5 mg/day MPA Control: • placebo
Duration of follow-up	3 years
Sources of funding	Industry funded (NV Organon)
Sample size	N=866

Study arms

Oestrogen + progestogen HRT (N = 284)

Placebo (N = 287)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 284	Placebo, N = 287

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(There is no information about concealment of the allocation sequence limited information on randomisation (participants were assigned code numbers in the order of their randomization into the study), however any baseline differences observed between intervention groups appear to be compatible with chance.)*
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)	Some concerns *(The study is described as double blind so it is likely that participants, carers and people delivering the interventions were unaware of intervention groups during the trial however this is unclear and there is no information on whether*

Section	Question	Answer
		there were deviations from intended intervention because of the trial context. It appears than an appropriate analysis was not used to estimate the effect of assignment to intervention however the potential impact (on the estimated effect of intervention) of the failure to analyse participants in the group to which they were randomized was not substantial.)
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)	High *(Participants, carers and people delivering the interventions were likely unaware of intervention groups during the trial however failures in implementing the intervention could have affected the outcome. It appears that an appropriate analysis was not used to estimate the effect of adhering to intervention.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Outcome data were not available for all, or nearly all, randomized participants. There is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value however it is not likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the assessment of the outcome is likely not to have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome*

Section	Question	Answer
		data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	High *(The study is at high risk of bias due to deviations from the intended interventions (effect of adhering to intervention) and some concerns of bias due to the randomisation process, deviations from the intended interventions (effect of assignment to intervention) and missing outcome data.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Liang, 2021

Bibliographic Reference	Liang, Ying; Jiao, Haoyan; Qu, Lingbo; Liu, Hao; Association Between Hormone Replacement Therapy and Development of Endometrial Cancer: Results from a Prospective US Cohort Study.; Frontiers in medicine; 2021; vol. 8; 802959

Study details

Country/ies where study was carried out	China
Study type	Prospective cohort study
Study dates	1993 to 2001
Inclusion criteria	• Postmenopausal women without hysterectomy aged 55-74 years
Exclusion criteria	• hysterectomy before the trial • did not return baseline questionnaires • cancer history before completing supplemental questionnaire • < 6 months follow-up after questionnaire completion or no follow up data

Patient characteristics	**Age (years)- Median (IQR)** No HRT: 73 (67–77) Current users: 68 (65–73) **BMI (kg/m2)- n (%)** No HRT: • <18.5: 189 (1.0) • 18.5–25 4: 163 (22.8) • 25–30: 4,045 (22.1) • >30: 3,103 (17.0) • Unknown: 6,786 (37.1) Current users: • <18.5: 222 (1.2) • 18.5–25: 6,529 (34.2) • 25–30: 4,798 (25.1) • >30: 2,616 (13.7) Unknown: 4,926 (25.8) **Ethnicity- n (%)** No HRT: • White, non-Hispanic: 15,858 (86.7) • Black, non-Hispanic: 1,360 (7.4) • Hispanic: 277 (1.5) • Asian: 625 (3.4) • Other: 158 (0.9) • Unknown: 8 (0.0) Current users: • White, non-Hispanic: 1,7445 (91.4) • Black, non-Hispanic: 426 (2.2) • Hispanic: 237 (1.2) • Asian: 877 (4.6)

	• Other: 102 (0.5) • Unknown: 4 (0.0) **Age at menopause (years)- n (%)** No HRT: • <40: 433 (2.4) • 40–44: 1,659 (9.1) • 45–49: 4,808 (26.3) • 50–54: 9,008 (49.3) • ≥55: 2,267 (12.4) • Unknown: 111 (0.6) Current users: • <40: 270 (1.4) • 40–44: 1,201 (6.3) • 45–49: 4,096 (21.5) • 50–54: 9,279 (48.6) • ≥55: 3,917 (20.5) • Unknown: 328 (1.7) **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (birth control pills)- n (%)** No HRT: • No: 10,470 (57.3) • Yes: 7,788 (42.6) • Unknown: 28 (0.2) Current users: • No: 6,984 (36.6) • Yes: 12,099 (63.4) • Unknown: 8 (0.0)

	Hysterectomy before menopause N/A (women with hysterectomy excluded) **Family history of cancer- n (%)** No HRT: No: 17,448 (95.4) Yes: 482 (2.6) Possible: (2.0) Current users: No: 18,281 (95.8) Yes: 527 (2.8) Possible: (1.4)
Intervention(s)/control	Intervention: • Oestrogen + progestogen HRT • Oestrogen-only HRT Control: • No HRT
Duration of follow-up	Mean: 11.6
Sources of funding	Not industry funded
Sample size	N=45203
Other information	Confounders: • age • age at menopause • body mass index • education • race • physical activity

	• family history of endometrial cancer • birth control pills

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen-only HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen-only HRT, N = NR	Placebo, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcome)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Manson, 2014

Bibliographic Reference	Manson, J.E.; Chlebowski, R.T.; Stefanick, M.L.; Aragaki, A.K.; Rossouw, J.E.; Prentice, R.L.; Anderson, G.; Howard, B.V.; Thomson, C.A.; Lacroix, A.Z.; Wactawski-Wende, J.; Jackson, R.D.; Limacher, M.; Margolis, K.L.; Wassertheil-Smoller, S.; Beresford, S.A.; Cauley, J.A.; Eaton, C.B.; Gass, M.; Hsia, J.; Johnson, K.C.; Kooperberg, C.; Kuller, L.H.; Lewis, C.E.; Liu, S.; Martin, L.W.; Ockene, J.K.; O'sullivan, M.J.; Powell, L.H.; Simon, M.S.; Van Horn, L.; Vitolins, M.Z.; Wallace, R.B.; Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials; Obstetrical and Gynecological Survey; 2014; vol. 69 (no. 2); 83-85

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998

Inclusion criteria	• postmenopausal women aged 50 to 79 years
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean±SD** Mean age: 63.2, SD: NR CEE plus MPA: 63.2 (7.1) Placebo: 63.3 (7.1) and 63.6 (7.3) CEE alone: 63.6 (7.3) **BMI (kg/m2)- median (IQR)** CEE plus MPA: 27.5 (24.2-31.7) Placebo: 27.5 (24.3-31.7) and 29.2 (25.7-33.5) CEE alone: 29.2 (25.7-33.7) **Ethnicity- n (%)** CEE plus MPA: • White: 7141 (84.0) • Black: 548 (6.4) • Hispanic: 471 (5.5) • American Indian: 25 (0.3) • Asian/Pacific Islander: 194 (2.3) • Unknown: 127 (1.5) Placebo: • White: 6805 (84.0) & 4075 (75.1) • Black: 574 (7.1) & 835 (15.4) • Hispanic: 415 (5.1) & 332 (6.1) • American Indian: 30 (0.4) & 34 (0.6) • Asian/Pacific Islander: 169 (2.1) & 78 (1.4) • Unknown: 109 (1.3) & 75 (1.4) CEE alone: • White: 4009 (75.5)

	• Black: 781 (14.7) • Hispanic: 319 (6.0) • American Indian: 41 (0.8) • Asian/Pacific Islander: 86 (1.6) • Unknown: 74 (1.4) **Time since menopause (years)- n (%)** **<10** CEE plus MPA: 2780 (36.2) Placebo: 2711 (36.1) and 817 (17.6) CEE alone: 827 (18.4) **10-<20** CEE plus MPA:3049 (39.7) Placebo: 2992 (39.9) and 1500 (32.4) CEE alone: 1438 (32.0) **≥20** CEE plus MPA: 1850 (24.1) Placebo: 1805 (24.0) and 2319 (50.0) CEE alone: 2230 (49.6) **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** **Never** CEE plus MPA: 6277 (73.8) Placebo: 6022 (74.4) & 2769 (51.0) CEE alone: 2769 (52.2) **Past** CEE plus MPA: 1671 (19.7) Placebo: 1587 (19.6) & 1947 (35.9) CEE alone: 1871 (35.2)

	Current CEE plus MPA: 554 (6.5) Placebo: 490 (6.1) & 709 (13.1) CEE alone: 669 (12.6) **Hysterectomy before menopause (age at time of hysterectomy, years)- n (%)** CEE plus MPA: Not reported Placebo: <40: 2148 (39.8) 40-49: 2275 (42.2) 50-54: 566 (10.5) ≥55: 404 (7.5) CEE alone: <40: 2100 (39.8) 40-49: 2280 (43.2) 50-54: 501 (9.5) ≥55: 401 (7.6) **Family history of cancer (breast cancer)- n (%)** CEE plus MPA: 1286 (16) Placebo: 1175 (15.3) & 870 (17.1) CEE alone: 892 (17.9)
Intervention(s)/control	CEE plus MPA oral CEE (0.625mg/d) plus MPA (2.5 mg/d) (Prempro) CEE alone oral CEE (0.625 mg/d) alone (Premarin) Placebo placebo
Duration of follow-up	CEE plus MPA trial The cumulative results include a median postintervention follow-up of 8.2 years (IQR, 6.6-8.2 years) and a median cumulative follow-up of 13.2 years (IQR, 10.5-14.2 years)

	CEE alone trial The cumulative results include a median postintervention follow-up was 6.6 years (IQR, 3.8-6.6 years) and the median cumulative follow-up of13.0 years (IQR, 9.1-14.1 years)
Sources of funding	Not industry funded
Sample size	N=27347
Other information	16,608 women with a uterus were randomized to oral CEE (0.625mg/d) plus MPA (2.5 mg/d) (Prempro) or placebo and 10,739 women with prior hysterectomy were randomized to oral CEE (0.625 mg/d) alone (Premarin) or placebo.

Study arms

Oestrogen + progestogen HRT (N = 8506)

Oestrogen-only HRT (N = 5310)

Placebo (N = 13531)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 8506	Oestrogen-only HRT, N = 5310	Placebo, N = 13531

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*

Section	Question	Answer
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Mørch, 2016

Bibliographic Reference	Mørch L; Kjaer S; Keiding N; Løkkegaard E; Lidegaard Ø; Kjær S; The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study; International Journal of Cancer; 2016; vol. 136 (no. 6); 1506-1515

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	1995 to 2009
Inclusion criteria	• aged 15–79 years
Exclusion criteria	• previous cancer • subsequent risk of endometrial cancer
Patient characteristics	Not reported in a usable format
Intervention(s)/control	Intervention: • oestrogen plus progestogen • oestrogen-only Control: • no HRT
Duration of follow-up	Mean follow up: 9.8 years
Sources of funding	Not industry funded
Sample size	N=914595
Other information	Confounders: • age • calendar year

	• education • hypertension • diabetes • parity

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen-only HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen-only HRT, N = NR	No HRT, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias for measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Nachtigall, 1979

Bibliographic Reference	Nachtigall, L E; Nachtigall, R H; Nachtigall, R D; Beckman, E M; Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems.; Obstetrics and gynecology; 1979; vol. 54 (no. 1); 74-9

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1956 to ~1976

Inclusion criteria	female hospitalized patients, patients had to have had their last menstrual period 2 or more years previously, to have never undertaken hormone replacements, to have elevated follicle-stimulating hormone levels >105.5mU by biological assay and to have total urinary oestrogen levels <10ug/dl as measured by the Smith modification of the Brown method
Exclusion criteria	Patients with acute heart disease, hypertension with blood pressure recording of 160/94, any apparent malignancy or a prior hysterectomy.
Patient characteristics	**Age (years)- mean** Mean age: 55.1, SD: NR Treated group: 55.3 Control group: 54.9 **BMI (kg/m2)- mean±SD** **Ethnicity (%)** **White** Treated group: 70 Control group: 69 **Black** Treated group: 30 Control group: 31 **Age at menopause (years)- mean±SD** Not reported **Mean years since last menstrual period (years)- mean** Treated group: 4.7 Control group: 4.5 **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Treatment group

	Conjugated oestrogen (Premarin), 2.5mg daily and medroxyprogesterone acetate (provera), 10mg daily for 7 days in each month Control group Placebo matching the active medications in appearance
Duration of follow-up	10 years
Sources of funding	Not reported
Sample size	N=168

Study arms

Oestrogen + progestogen HRT (N = 84)

Placebo (N = 84)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 84	Placebo, N = 84

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(The allocation sequence was not adequately concealed (the research nurse randomly elected which member of each pair would be assigned to treatment or control group).)*
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)	High *(The code was broken 13 times in the treatment group and 17 times in the control group (which was unbalanced between the groups) and meant that participants, carers or people delivering the interventions were likely aware of intervention groups during the trial. These deviations from intended interventions likely arose because of the trial context and were likely to have affected the outcome.)*

Section	Question	Answer
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)	High *(It is likely that participants, carers or people delivering the interventions were aware of intervention groups. It is unclear whether the important non-protocol interventions were balanced across intervention groups, and it is unclear whether an appropriate analysis was not used to estimate the effect of adhering to intervention.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(The method of measuring the outcome was not inappropriate and the measurement or ascertainment of the outcome did not appear to differ between intervention groups. It is unlikely that the assessment of the outcome could have been influenced by knowledge of the intervention received and it is unlikely that assessment of the outcome was influenced by knowledge of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(There is no information on whether the result being assessed is likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	High *(The study has high risk of bias due to the randomisation process, deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention) and some concerns of bias due to measurement of the outcomes and in the selection of the reported result.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Obel, 1993

Bibliographic Reference	Obel, E B; Munk-Jensen, N; Svenstrup, B; Bennett, P; Micic, S; Henrik-Nielsen, R; Nielsen, S P; Gydesen, H; Jensen, B M; A two-year double-blind controlled study of the clinical effect of combined and sequential postmenopausal replacement therapy and steroid metabolism during treatment.; Maturitas; 1993; vol. 16 (no. 1); 13-21

Study details

Country/ies where study was carried out	Denmark
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• women born between 1930 and 1933 • living in Frederiksborg County • early menopause (last spontaneous • vaginal bleeding more than 6 and less than 24 months earlier) • no HRT during the preceding 24 months
Exclusion criteria	• previous or current oestrogen-dependent neoplasia • thromboembolic disease • liver or pancreatic disease • diabetes mellitus • severe obesity • diseases with high or low bone turnover • medication known to influence bone metabolism or provoke induction of liver enzymes.
Patient characteristics	**Age (years)- mean±SD** Not reported **BMI (kg/m2)- mean±SD** Not reported **Ethnicity** Not reported

	Age at menopause (years)- mean±SD Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • 2 mg oestradiol plus 1 mg norethisterone acetate • sequential therapy (2 mg E2 for 12 days, 2 mg E, and 1 mg NETA for 10 days and 1 mg E, for 6 days) Control: • placebo
Duration of follow-up	2 years
Sources of funding	Not reported
Sample size	N=151

Study arms

Oestrogen + progestogen HRT (combined) (N = 50)

Oestrogen + progestogen HRT (sequential) (N = 50)

Placebo (N = 51)

Outcomes

Outcome	Oestrogen + progestogen HRT (combined), N = 50	Oestrogen + progestogen HRT (sequential) , N = 50	Placebo, N = 51

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(There is no information about concealment of the allocation sequence and randomisation. There is limited information on baseline differences, and it is difficult to determine whether there is a problem with the randomisation process.)*
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)	Some concerns *(The study is described as double blind; however no further information is provided. Participants, carers and people delivering the interventions were likely unaware of intervention groups during the trial and an appropriate (intention to treat) analysis was used to estimate the effect of assignment to intervention.)*
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)	Some concerns *(It is likely that participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate (intention to treat) analysis was used to estimate the effect of adhering to intervention.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Outcome data were not available for all, or nearly all, randomized participants. There is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value and it is not likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the assessment of the outcome is likely not to have been influenced by knowledge of the intervention received.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	High *(The study is at high risk of bias due to the randomisation process, and some concerns due to deviations from the intended interventions (effect of assignment to intervention and (effect of adhering to intervention) and missing outcome data.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

PEPI Writing Group 1995

Bibliographic Reference	PEPI Writing Group 1995; Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.; JAMA; 1996; vol. 275 (no. 5); 370-5

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• Aged 45 to 64 years

	• no menses at least 1 year but not more than 10 years prior to enrolment • follicle-stimulating hormone level of at least 40 IU/L • normal or atrophic endometrial biopsy result at baseline
Exclusion criteria	• breast or endometrial cancer, any other cancer except non-melanomatous skin cancer (diagnosed < 5 years before baseline) • serious medical illness • severe menopausal symptoms
Patient characteristics	**Age (years)- mean** 56.2 **BMI (kg/m2)- mean** 25.7 **Ethnicity- (%)** • White: 91% • African American: 4% • Hispanic: 3% • Other: 2% **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT (use of oestrogen, ever)- %** 49% **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • 0.625 mg/day CEE

	• 0.625 mg/day CEE plus 2.5 mg/day MPA • 0.625 mg/day CEE plus 10 mg/day MPA for the first 12 days • 0.625 mg/day CEE plus 200 mg/day MP for the first 12 days Control: • placebo
Duration of follow-up	3 years
Sources of funding	Not industry funded
Sample size	N=596 0.625 mg/day CEE: n=119 0.625 mg/day CEE plus 2.5 mg/day MPA: n=120 0.625 mg/day CEE plus 10 mg/day MPA for the first 12 days: n=118 0.625 mg/day CEE plus 200 mg/day MP for the first 12 days: n=120 Placebo: n=119

Study arms

Oestrogen-only HRT (N = 119)

Oestrogen + progestogen HRT (continuous) (N = 120)

Oestrogen + progestogen HRT (cyclic) (N = 118)

Oestrogen + progestogen HRT (MP, continuous) (N = 120)

Placebo (N = 119)

Outcomes

Outcome	Oestrogen-only HRT, N = 119	Oestrogen + progestogen HRT (continuous), N = 120	Oestrogen + progestogen HRT (cyclic), N = 118	Oestrogen + progestogen HRT (MP, continuous), N = 120	Placebo, N = 119

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated randomisation, developed and installed by the PEPI Coordinating Centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate (intention to treat) analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Prentice, 2009

Bibliographic Reference	Prentice, Ross L; Manson, Joann E; Langer, Robert D; Anderson, Garnet L; Pettinger, Mary; Jackson, Rebecca D; Johnson, Karen C; Kuller, Lewis H; Lane, Dorothy S; Wactawski-Wende, Jean; Brzyski, Robert; Allison, Matthew; Ockene, Judith; Sarto, Gloria; Rossouw, Jacques E; Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause.; American journal of epidemiology; 2009; vol. 170 (no. 1); 12-23

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT) Prospective cohort study
Study dates	1993 to 2004
Inclusion criteria	postmenopausal women aged 50 to 79 years without hysterectomy
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean±SD** Mean age: 63.2, SD: NR Oestrogen +progestogen HRT: 55.2 (2.6) Placebo: 55.3 (2.6) **BMI (kg/m2)- mean±SD** Oestrogen + progestogen HRT: 27.7 (7.9)

	Placebo: 27.8 (8.2) **Ethnicity- n (%)** Oestrogen + progestogen HRT: • White: 2,192 (77.3) • Black: 255 (9.0) • Hispanic: 265 (9.3) • American Indian: 11 (0.4) • Asian/Pacific Islander: 68 (2.4) • Unknown: 46 (1.6) Placebo: • White: 2061 (76.8) • Black: 279 (10.4) • Hispanic: 226 (8.4) • American Indian: 16 (0.6) • Asian/Pacific Islander: 63 (2.3) • Unknown: 38 (1.4) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n (%)** **CEE alone** Never used: 841 (51.3) Past user: 513 (31.3) Current user: 285 (17.4) **Placebo** Never used: 831 (49.6) & 1951 (72.7) Past user: 531 (31.7) & 482 (18.0) Current user: 312 (18.6) & 250 (9.3)

	CEE plus MPA Never used: 1983 (69.9) Past user: 553 (19.5) Current user: 301 (10.6) **Hysterectomy before menopause** Not reported **Family history of cancer (breast cancer, female relative)- n (%)** CEE alone: 285 (18.5) Placebo: 261 (16.4) & 371 (14.6) • CEE plus MPA: 403 (14.9)
Intervention(s)/control	Intervention: • 0.625 mg/day CEE plus 2.5 mg/day MPA Control: • placebo
Duration of follow-up	Median follow up: 5.5 years
Sources of funding	Not industry funded
Sample size	N=15188

Study arms

Oestrogen and progestogen HRT (N = NR)

Placebo (N = NR)

Outcomes

Outcome	Oestrogen and progestogen HRT, N = NR	Placebo, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Prentice, 2021

Bibliographic Reference	Prentice, Ross L; Aragaki, Aaron K; Chlebowski, Rowan T; Rossouw, Jacques E; Anderson, Garnet L; Stefanick, Marcia L; Wactawski-Wende, Jean; Kuller, Lewis H; Wallace, Robert; Johnson, Karen C; Shadyab, Aladdin H; Gass, Margery; Manson, JoAnn E; Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone Therapy Among Women 50-59 Years of Age.; American journal of epidemiology; 2021; vol. 190 (no. 3); 365-375

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2004
Inclusion criteria	• postmenopausal women aged 50 to 59 years without hysterectomy
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- mean±SD** Mean age: 55.2, SD: NR Oestrogen +progestogen HRT: 55.2 (2.6) Placebo: 55.3 (2.6) **BMI (kg/m2)- mean±SD** Oestrogen + progestogen HRT: 27.7 (7.9)

	Placebo: 27.8 (8.2) **Ethnicity- n (%)** Oestrogen + progestogen HRT: • White: 2,192 (77.3) • Black: 255 (9.0) • Hispanic: 265 (9.3) • American Indian: 11 (0.4) • Asian/Pacific Islander: 68 (2.4) • Unknown: 46 (1.6) Placebo: • White: 2061 (76.8) • Black: 279 (10.4) • Hispanic: 226 (8.4) • American Indian: 16 (0.6) • Asian/Pacific Islander: 63 (2.3) • Unknown: 38 (1.4) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n (%)** **CEE alone** Never used: 841 (51.3) Past user: 513 (31.3) Current user: 285 (17.4) **Placebo** Never used: 831 (49.6) & 1951 (72.7) Past user: 531 (31.7) & 482 (18.0) Current user: 312 (18.6) & 250 (9.3)

	CEE plus MPA Never used: 1983 (69.9) Past user: 553 (19.5) Current user: 301 (10.6) **Hysterectomy before menopause** Not reported **Family history of cancer (breast cancer, female relative)- n (%)** CEE alone: 285 (18.5) Placebo: 261 (16.4) & 371 (14.6) CEE plus MPA: 403 (14.9)
Intervention(s)/control	Intervention: • 0.625 mg/day CEE plus 2.5 mg/day MPA Control: • placebo
Duration of follow-up	Median cumulative follow-up of 18 years
Sources of funding	Not industry funded
Sample size	N=5520

Study arms

Oestrogen + progestogen HRT (N = 8506)

Placebo (N = 8102)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 8506	Placebo, N = 8102

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate (intention to treat analysis) was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable

Section	Question	Answer
Overall bias and directness	Risk of bias variation across outcomes	None

Rossouw, 2002

Bibliographic Reference Rossouw, Jacques E; Anderson, Garnet L; Prentice, Ross L; LaCroix, Andrea Z; Kooperberg, Charles; Stefanick, Marcia L; Jackson, Rebecca D; Beresford, Shirley A A; Howard, Barbara V; Johnson, Karen C; Kotchen, Jane Morley; Ockene, Judith; Writing Group for the Women's Health Initiative, Investigators; Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.; JAMA; 2002; vol. 288 (no. 3); 321-33

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	• aged 50-79 years with an intact uterus • postmenopausal • likelihood of residence in the area for 3 years • provision of written informed consent
Exclusion criteria	• any medical condition with a predicted survival of <3 years • prior breast cancer • other prior cancer within the last 10 years except non-melanoma skin cancer • low hematocrit or platelet counts • substance misuse • dementia
Patient characteristics	**Age (years)- mean±SD** Mean age: 63.3, SD: NR

	Oestrogen + progestogen HRT: 63.2 (7.1) Placebo: 63.3 (7.1) **BMI (kg/m2)- mean±SD** Oestrogen + progestogen HRT: 28.5 (5.8) Placebo: 28.5 (5.9) **Ethnicity- n (%)** Oestrogen + progestogen HRT: • White: 7140 (83.9) • Black: 549 (6.5) • Hispanic: 472 (5.5) • American Indian: 26 (0.3) • Asian/Pacific Islander: 194 (2.3) • Unknown: 125 (1.5) Placebo: • White: 6805 (84) • Black: 575 (7.1) • Hispanic: 416 (5.1) • American Indian: 30 (0.4) • Asian/Pacific Islander: 169 (2.1) • Unknown: 107 (1.3) **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n (%)** Oestrogen + progestogen HRT: Never: 6280 (73.9) Past: 1674 (19.7) Current: 548 (6.4)

	Placebo: Never: 6024 (74.4) Past: 1588 (19.6) Current: 487 (6.0) **Hysterectomy before menopause** Not reported **Family history of cancer (breast cancer, female relative)- n (%)** Oestrogen + progestogen HRT: 1286 (16.0) Placebo: 1175 (15.3)
Intervention(s)/control	Intervention: • 0.625 mg/day CEE plus 2.5 mg/day MPA Control: • placebo
Duration of follow-up	Median follow-up 5.2 years
Sources of funding	Not industry funded
Sample size	N=16608

Study arms

Oestrogen + progestogen HRT (N = 8506)

Placebo (N = 8102)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = 8506	Placebo, N = 8102

Outcome: Incidence of endometrial cancer. See Appendix Lfor details on data.

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
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, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
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 *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Schneider, 2009

Bibliographic Reference	Schneider, C; Jick, S S; Meier, C R; Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations; Climacteric: the journal of the International Menopause Society; 2009; vol. 12 (no. 6); 514-24

Study details

Country/ies where study was carried out	United Kingdom
Study type	Prospective cohort study
Study dates	1987 to 2007
Inclusion criteria	None specified
Exclusion criteria	• History of any cancer • stroke • myocardial infarction • venous thromboembolism.
Patient characteristics	**Age (years) at follow up- N** Mean age (SD): 51.3 (6.1) Cases: <50: 3 50-59: 45

	60+: 29 Controls: <50: 20 50-59: 273 60+: 169 **BMI (kg/m2)- mean±SD** Cases: <25: 23 25–29.9: 18 30+: 26 Unknown: 10 Controls: <25: 179 25–29.9: 129 30+: 74 Unknown: 80 **Ethnicity** Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT- n** Cases: Progestins No: 73 Yes: 4 Vaginal oestrogens No: 74

	Yes: 3 Controls: Progestins No: 451 Yes: 11 Vaginal oestrogens No: 410 Yes: 52 **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • Group 1: Women who received at least one prescription for any dosage form of oestradiol/dydrogesterone below the age of 70, and never received a prescription for any other oestrogen-containing HRT. • Group 2: Frequency matched women (matched on year of first HRT prescription and age), who received at least 1 prescription for oral conjugated equine oestrogen (CEE) plus norgestrel, oral oestradiol plus norethisterone acetate or oral CEE plus MPA, and never received a prescription for any other HRT. Control: • Group 3: Frequency matched comparison group of women (matched on age) who have never received HRT prescriptions
Duration of follow-up	HRT users mean 6 years. Nonusers mean 5.7 years.
Sample size	N=602
Other information	Study does not specify if participants had bilateral oophorectomy or not.

Study arms

Oestrogen + progestogen HRT (N = 86)

No HRT (N = 516)

Outcomes

Outcome	Oestrogen + progestogen HRT (N = 86)	No HRT, N=516

Outcome: Incidence of endometrial cancer. See Appendix L for details on data. Note: Outcomes reported as IRR but interpreted as RR

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.4 ovarian cancer

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?	Smoking status, BMI, use of oral contraceptives, progesterone preparations and vaginal oestrogens.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No *(No adjustments for age at menopause)*
(B) What are the results?	7. What are the results of this study?	There is no difference in risk of ovarian cancer if taking hormonal replacement therapy
(B) What are the results?	8. How precise are the results?	Imprecise
(B) What are the results?	9. Do you believe the results?	Cannot confidently believe results due to not all confounders adjusted for and imprecise.

Section	Question	Answer
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell

Sponholtz, 2018

Bibliographic Reference	Sponholtz, Todd R; Palmer, Julie R; Rosenberg, Lynn A; Hatch, Elizabeth E; Adams-Campbell, Lucile L; Wise, Lauren A; Exogenous Hormone Use and Endometrial Cancer in U.S. Black Women.; Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; 2018; vol. 27 (no. 5); 558-565

Study details

Country/ies where study was carried out	US
Study type	Prospective cohort study
Study dates	1995 to 2013
Inclusion criteria	• aged 21-69
Exclusion criteria	• a history of uterine cancer, cervical cancer, or hysterectomy, and those from whom no follow-up questionnaire had been received
Patient characteristics	**Age (years)- mean±SD** HRT use: 36.6 (116.5) No HRT: 39.2 (170.8) **BMI (kg/m2)- mean±SD** HRT use: 29.0 (93.1) No HRT: 30.5 (109.8) **Ethnicity**

	Not reported **Age at menopause (years)- mean±SD** Not reported **Age at last menstrual period (years)- mean±SD** Not reported **Previous use of HRT, %** Ever use of oestrogen-only HRT use: 2.6 No HRT use: 3.4 Ever use of oestrogen + progestin HRT use: 8.7 No HRT use: 9.0 Ever use of progestin-only HRT use: 1.6 No HRT use: 1.1 **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • oestrogen plus progestogen • oestrogen-only Control: • no HRT
Duration of follow-up	Mean follow up: 14.5 years
Sources of funding	Not industry funded
Sample size	N=47555

Other information	Confounders: • age • study period • age at menarche • parity • menopausal status • oestrogen-only FMH use • oestrogen plus progestin FMH use • smoking • body mass index • vigorous physical activity

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen-only HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen-only HRT, N = NR	No HRT, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data. Note: Outcomes reported as IRR but interpreted as RR

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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*

Section	Question	Answer
		in the study and for each participant, start of follow up and start of intervention coincided.)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

Trabert, 2013

Bibliographic Reference	Trabert, Britton; Wentzensen, Nicolas; Yang, Hannah P; Sherman, Mark E; Hollenbeck, Albert R; Park, Yikyung; Brinton, Louise A; Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? International journal of cancer; 2013; vol. 132 (no. 2); 417-26

Study details

Country/ies where study was carried out	US
Study type	Prospective cohort study
Study dates	1995 to 1997
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Patient characteristics	**Age (years)- n (%)** No HRT: <57: 3,099 (8.7) 57–60: 6,625 (18.6) 61–64: 10,395 (29.2) 65–68: 13,873 (39.0) >=69: 1,588 (4.5) Oestrogen-only HRT: <57: 405 (8.4) 57–60: 819 (17) 61–64: 1329 (27.6) 65–68: 1967 (40.9) >=69: 290 (6) Oestrogen + progesterone: aggregate data unavailable **BMI (kg/m2)- n (%)** No HRT:

	< 25: 14,659 (41.2) 25-< 30: 11,216 (31.5) ≥30: 8,569 (24.1) Oestrogen-only HRT: < 25: 2,158 (44.9) 25-< 30: 1,536 (31.9) ≥30: 981 (20.4) Oestrogen + progesterone: aggregate data unavailable **Ethnicity- n (%)** No HRT: White: 32268 (90.7) Other: 3312 (9.3) Oestrogen-only HRT: White: 4401 (91.5) Other: 409 (8.5) Oestrogen + progesterone: aggregate data unavailable **Age at menopause (years)- n (%)** No HRT: <45: 4,391 (12.3) 45-49: 9890 (27.8) 50-54: 17358 (48.8) 55+: 3489 (9.8) Oestrogen-only HRT: <45: 718 (14.9) 45-49: 1461 (30.4) 50-54: 2121 (44.1) 55+: 421 (8.8) Oestrogen + progesterone: aggregate data unavailable **Age at last menstrual period (years)- mean±SD**

	Not reported **Previous use of HRT** Not reported **Hysterectomy before menopause** Not reported **Family history of cancer** Not reported
Intervention(s)/control	Intervention: • oestrogen + progestogen ○ sequential (progestin use for less than 15 days per month) • oestrogen-only Control: • no HRT
Duration of follow-up	Mean follow up 4.8 years for EC cases
Sources of funding	Not industry funded
Sample size	N=68419
Other information	Confounders: • age • race • duration of oral contraceptive use • use of other MHT formulations

Study arms

Oestrogen + progestogen HRT (N = NR)

Oestrogen HRT (N = NR)

No HRT (N = NR)

Outcomes

Outcome	Oestrogen + progestogen HRT, N = NR	Oestrogen HRT, N = NR	No HRT, N = NR

Outcome: Incidence of endometrial cancer. See Appendix L for details on data.

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(No confounding expected.)*
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 for each participant, start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Any deviations from usual practice were unlikely to impact on the outcome.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(The analysis addressed missing data and is likely to have removed any risk of bias)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Low risk of bias in measurement of outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub cohorts.)*

Section	Question	Answer
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	The study is judged to be at low risk of bias for all domains.
Overall bias	Directness	Directly applicable

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 endometrial cancer?

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

In some instances, where possible due to similarity of outcomes, observational evidence has been presented on the same forest plot as RCT evidence for so that they can be compared visually. Analyses remains separate for RCT evidence and observational evidence. Different effect estimates are analysed separately, but where it was deemed necessary for visualisation purposes they have been presented on the same plot, but specifics of each provided in the footnotes where applicable. Please refer to the footnotes of relevant forest plots for more information where this is the case.

Combined oestrogen and progestogen HRT- randomised controlled trials forest plots

Comparison 1: Combined oestrogen and progestogen HRT versus placebo

Figure 2: Current users, 1-4 years duration HRT: Incidence of endometrial cancer

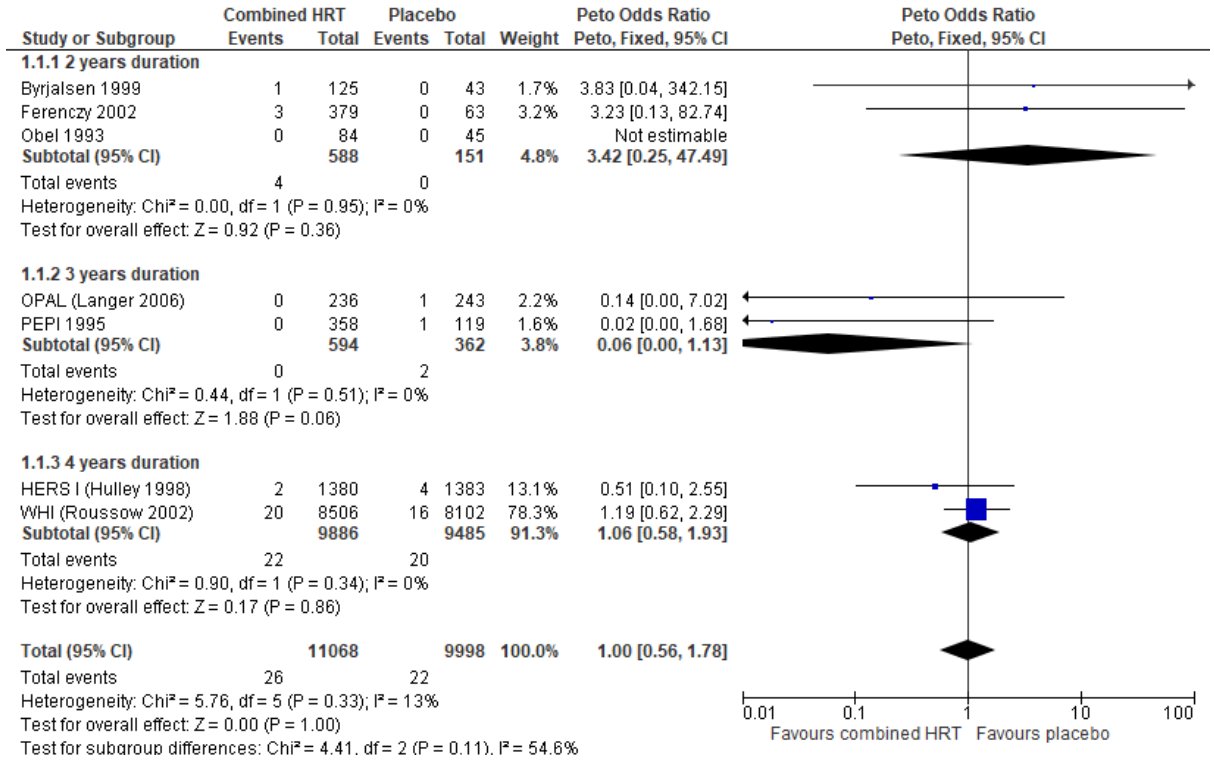


Figure 3: Current users, 1-4 years duration HRT by oestrogen constituent: Incidence of endometrial cancer

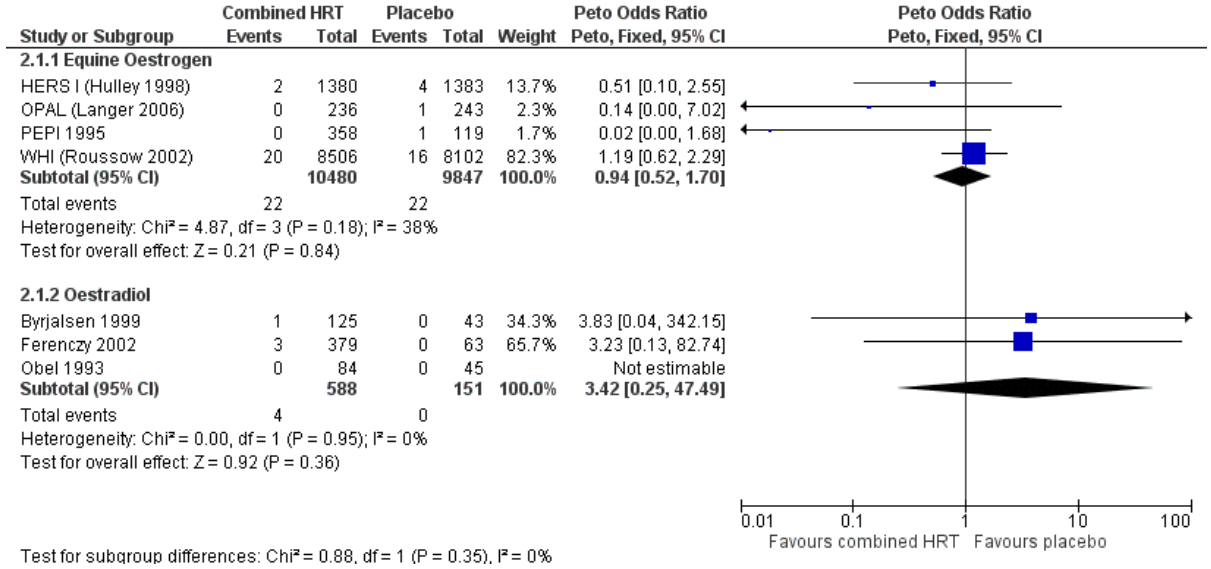


Figure 4: Current users, 1-4 years duration HRT by progestogenic constituent: Incidence of endometrial cancer

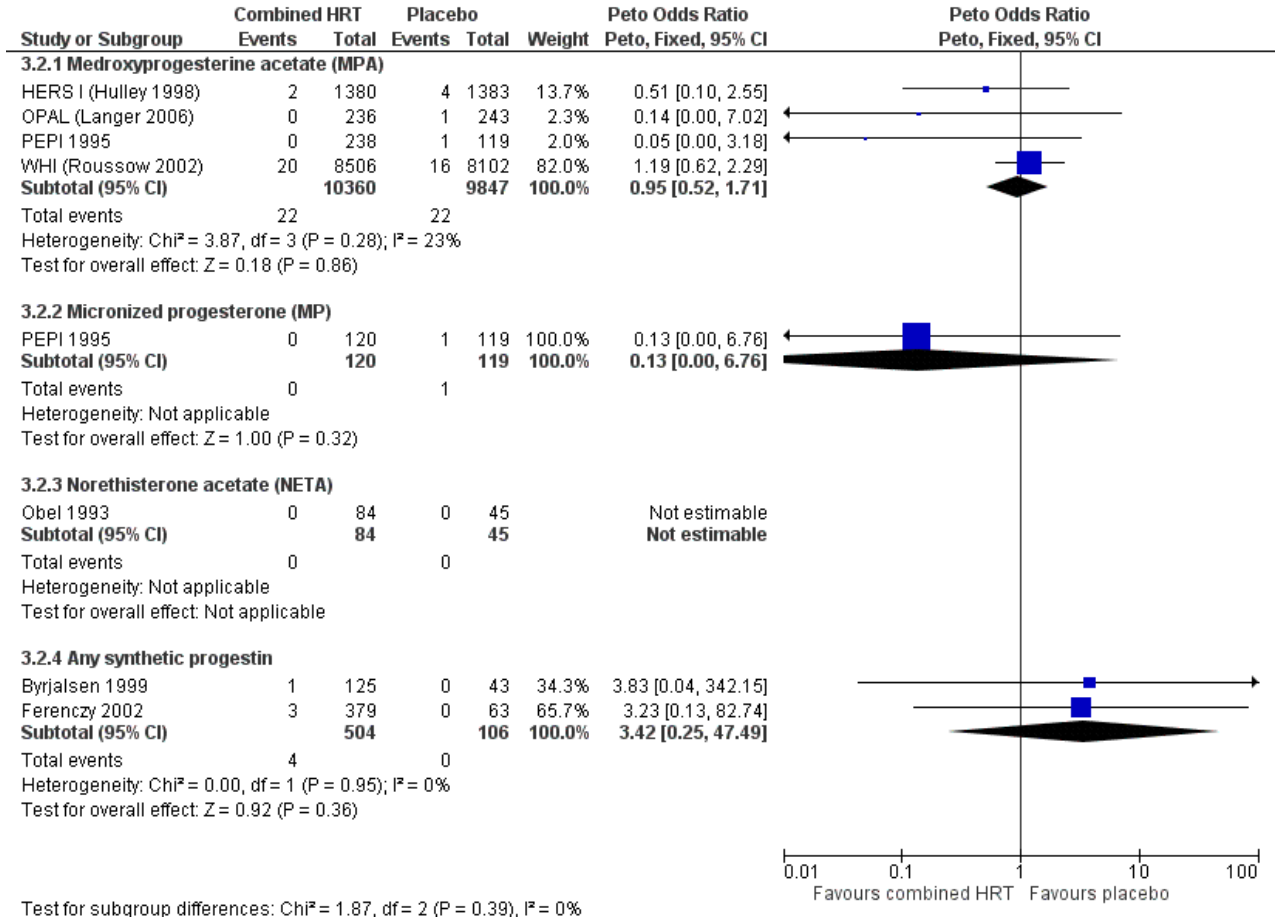


Figure 5: Current users, 1-4 years duration HRT with oestradiol by sequential dosage: Incidence of endometrial cancer

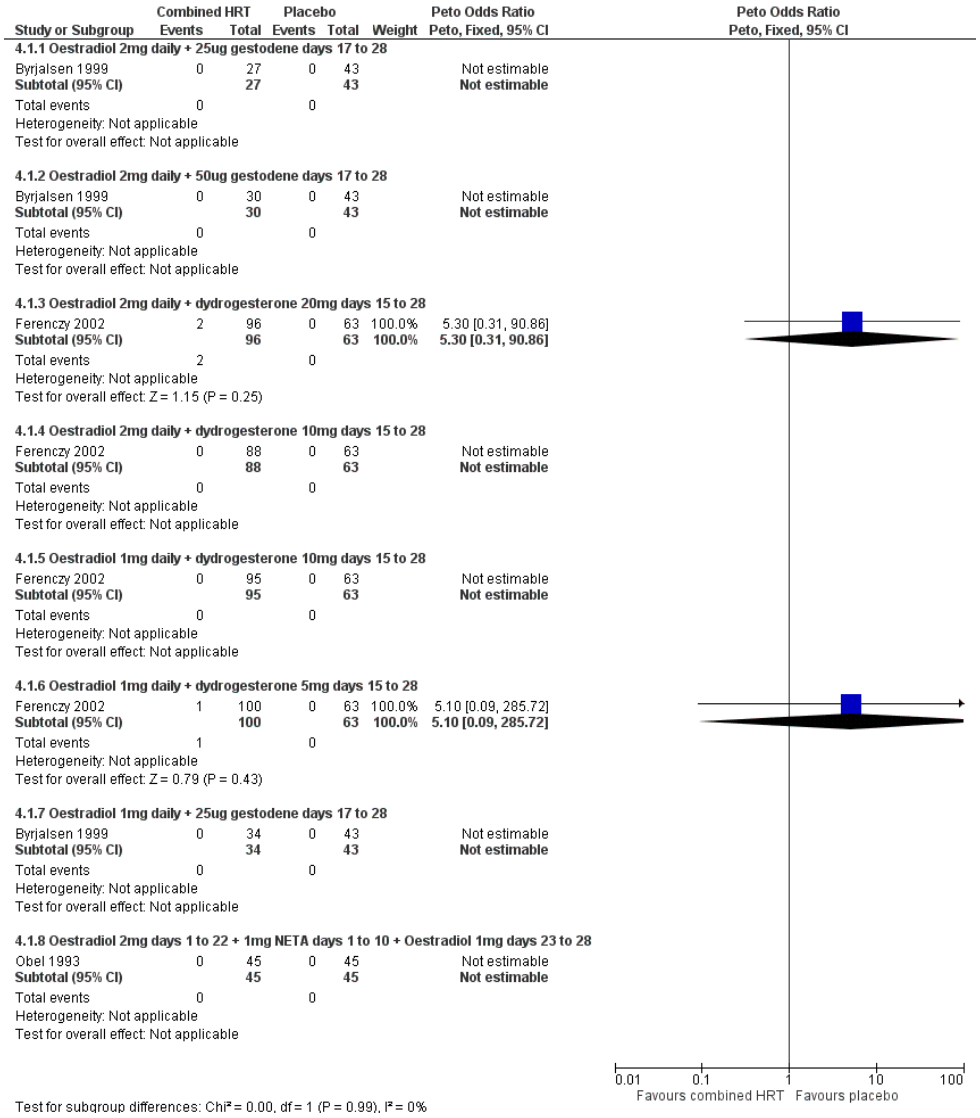


Figure 6: Current users, 1-4 years duration HRT with equine oestrogen by sequential dosage: Incidence of endometrial cancer

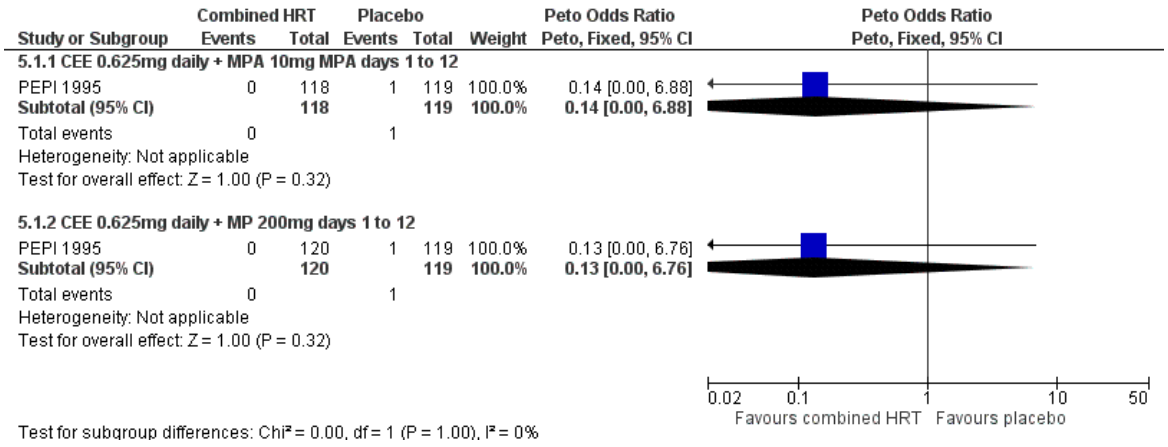


Figure 7: Current users, 5-9 years duration HRT by age at first use: Incidence of endometrial cancer

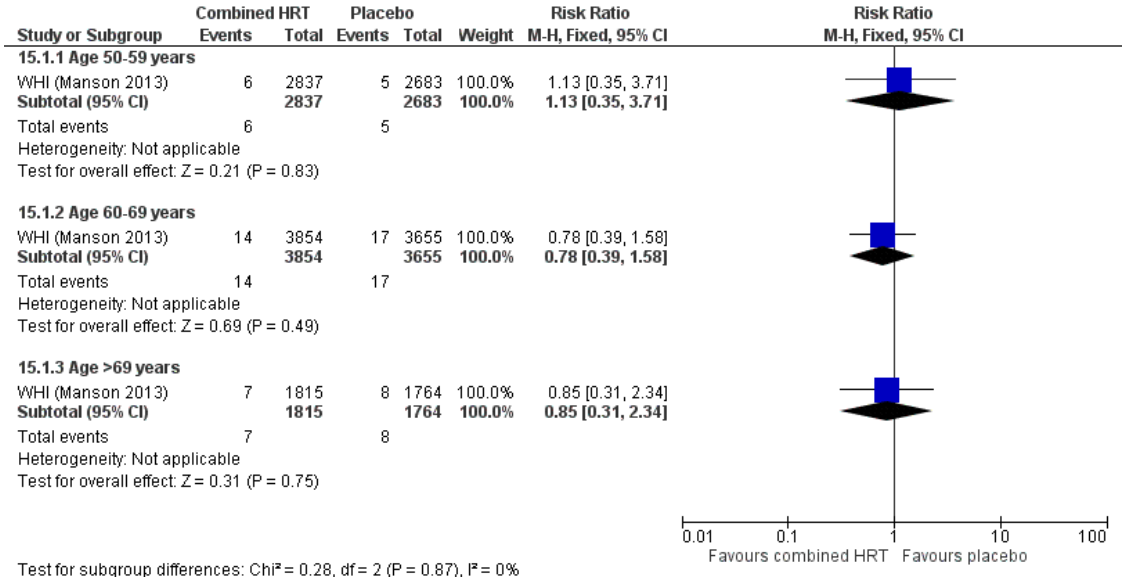


Figure 8: Current and past users (of variable recency), 5-9 years duration HRT: Incidence of endometrial cancer

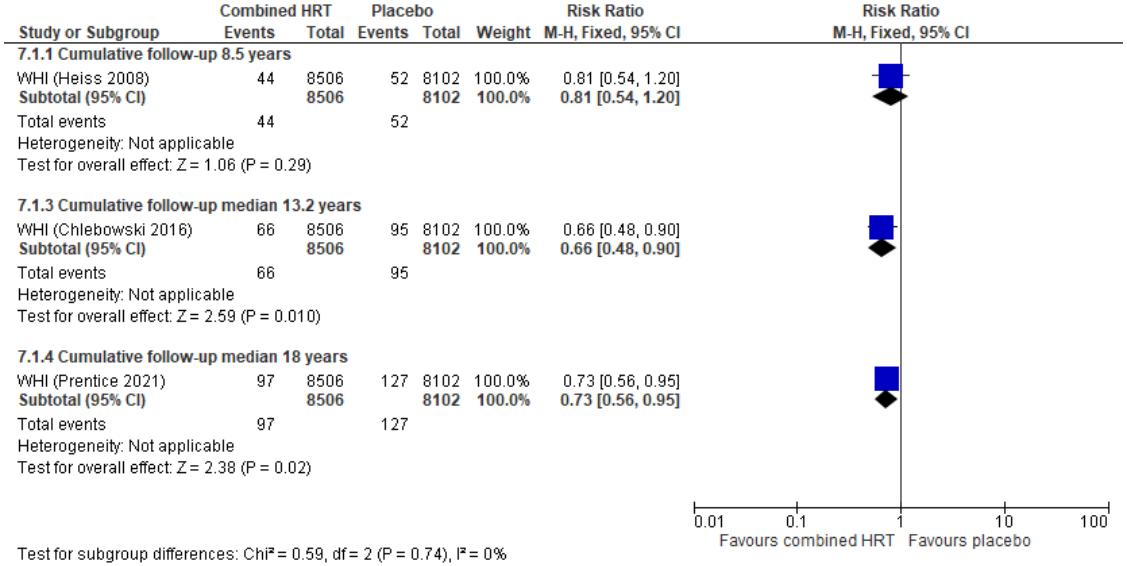


Figure 9: Current and past users, 5-9 years duration HRT by age at first use at 13.2 years follow-up: Incidence of endometrial cancer

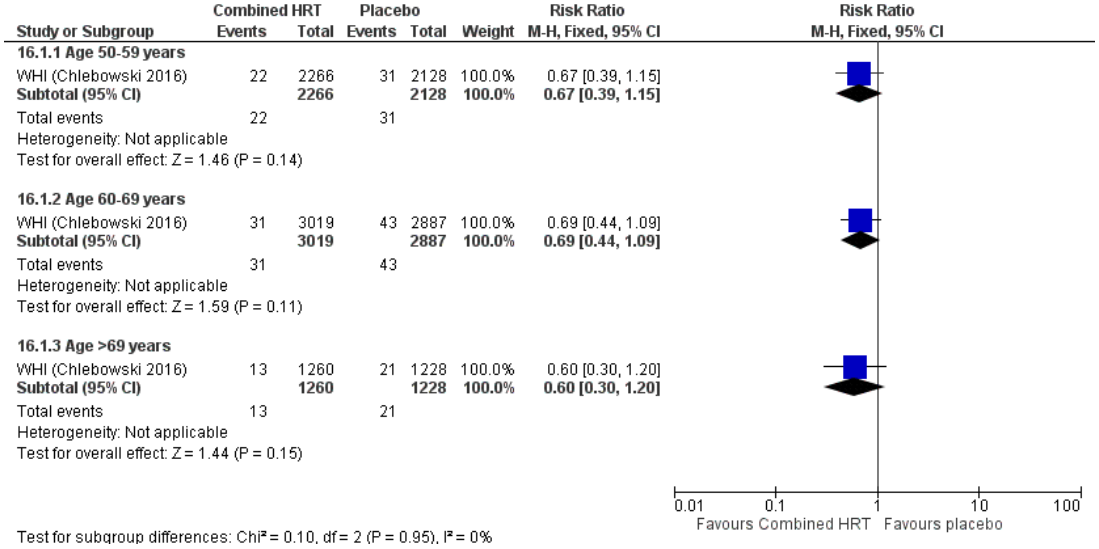


Figure 10: Current and past users, 5-9 years duration HRT by ethnicity at 13.2 years follow-up: Incidence of endometrial cancer

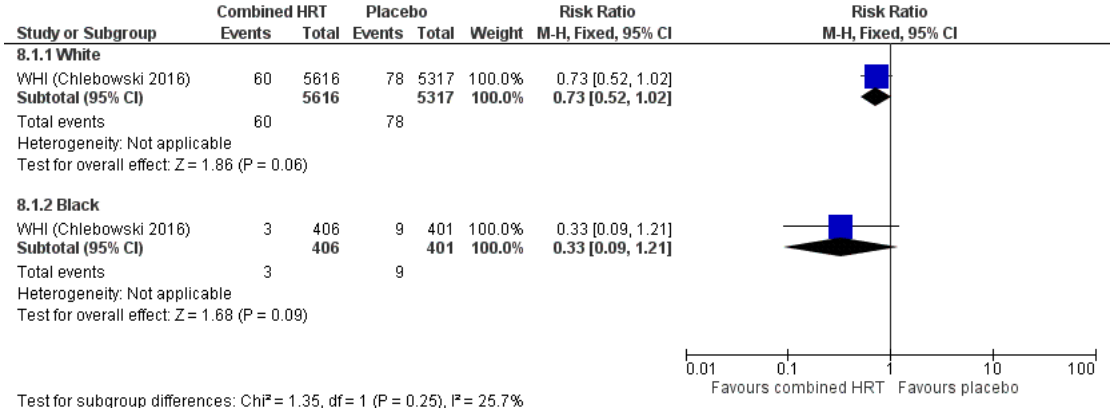
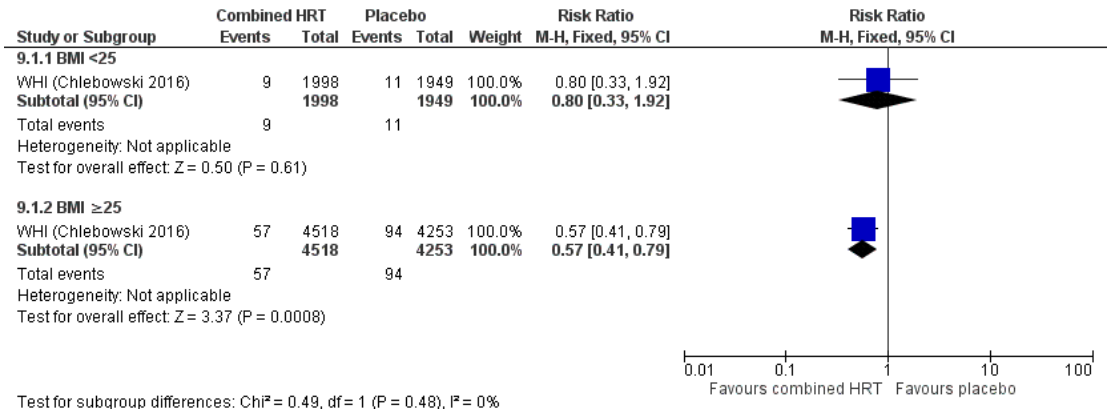


Figure 11: Current and past users, 5-9 years duration HRT by BMI at 13.2 years follow-up: Incidence of endometrial cancer



Combined oestrogen and progestogen HRT- observational studies forest plots

Comparison 2: Any combined oestrogen + progestogen HRT versus no HRT

Figure 12: Incidence of endometrial cancer- current users, duration of use, HR

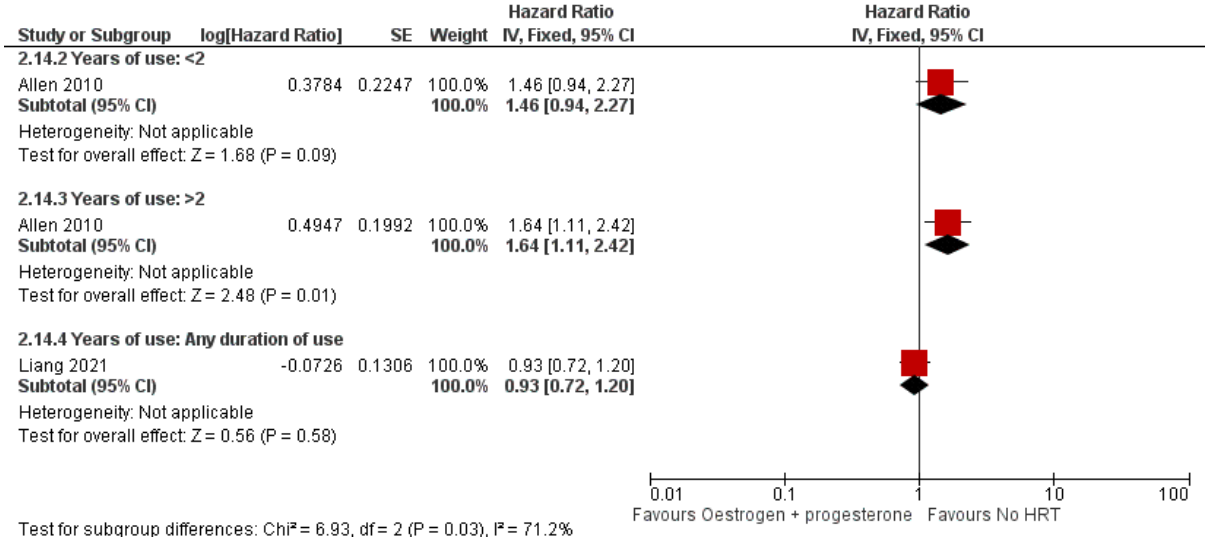


Figure 13: Incidence of endometrial cancer – current users, duration of use RR (observational and RCT)

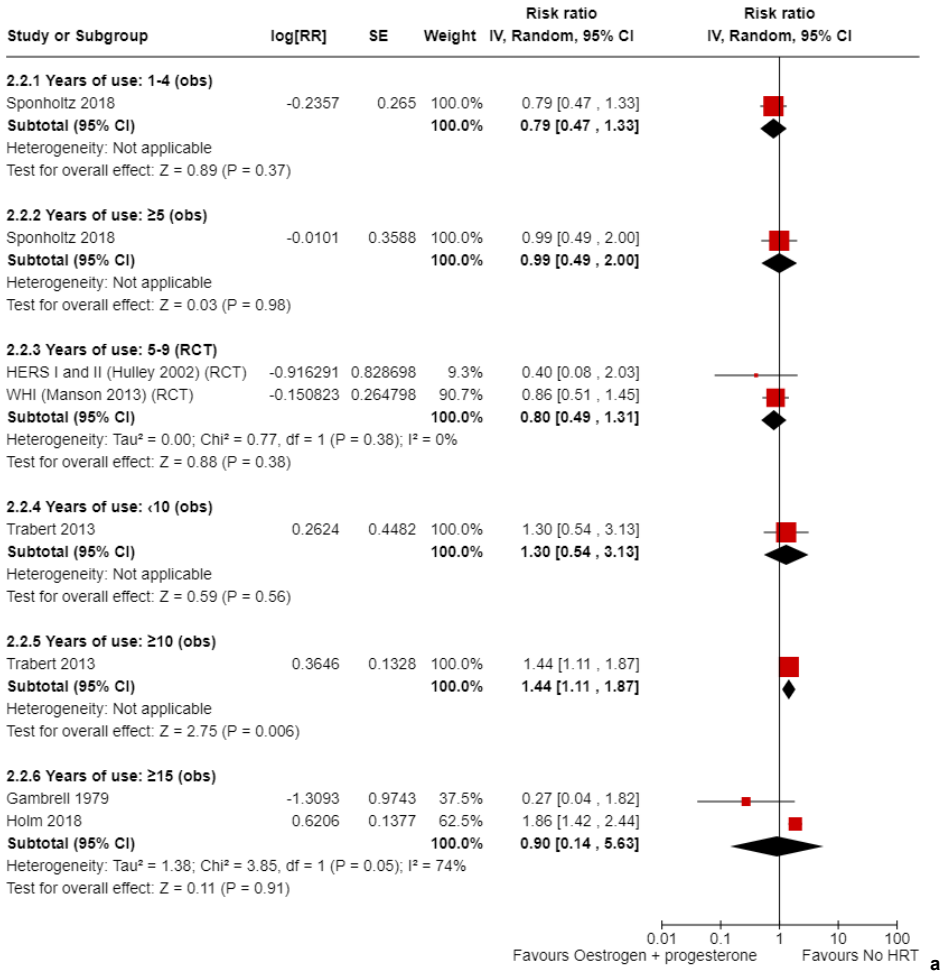
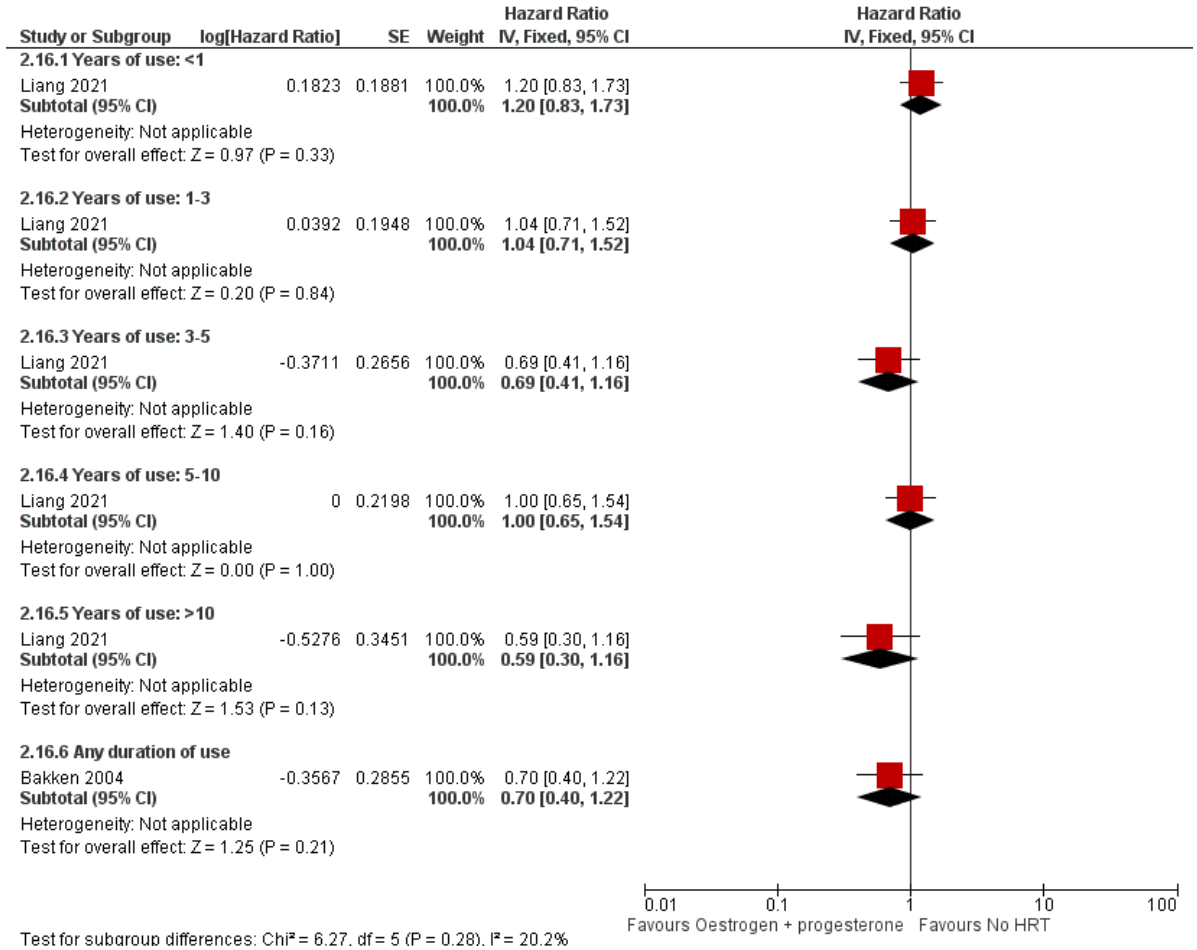


Figure 14: Incidence of endometrial cancer – all users, duration of use HR



[a] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. See table 10 for full GRADE profile for RCT evidence, and table 19 for full GRADE profile of observational evidence. Test for subgroup differences for observational evidence: Chi² = 8.83, df = 4 (P = 0.07), I² = 54.7%

Figure 15: Incidence of endometrial cancer – current users, by constituent, any duration of use, HR

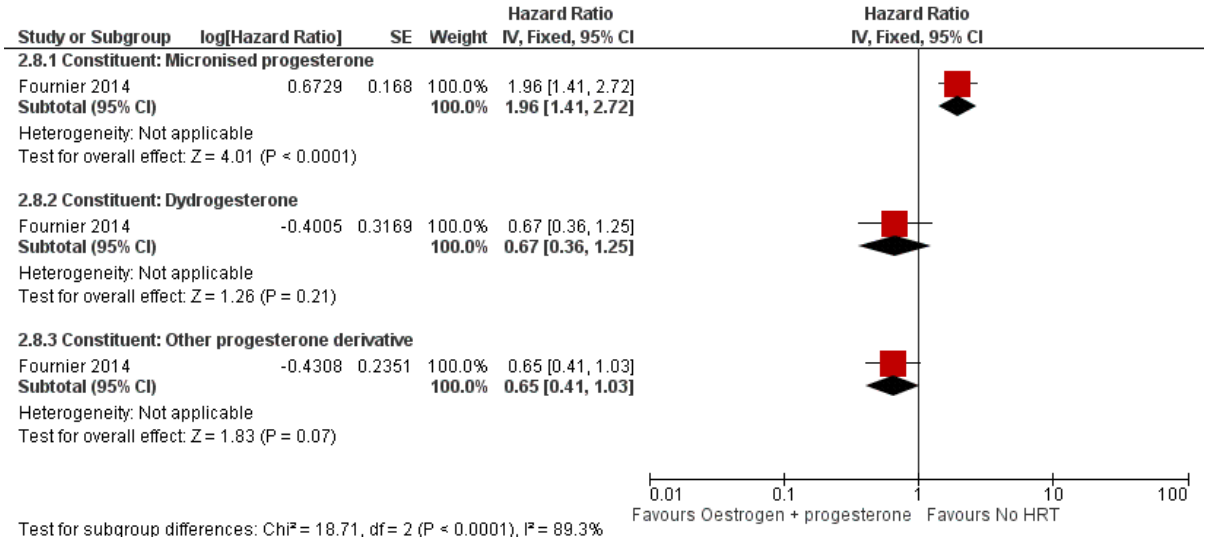


Figure 16: Incidence of endometrial cancer – all users, by constituent, any duration, OR

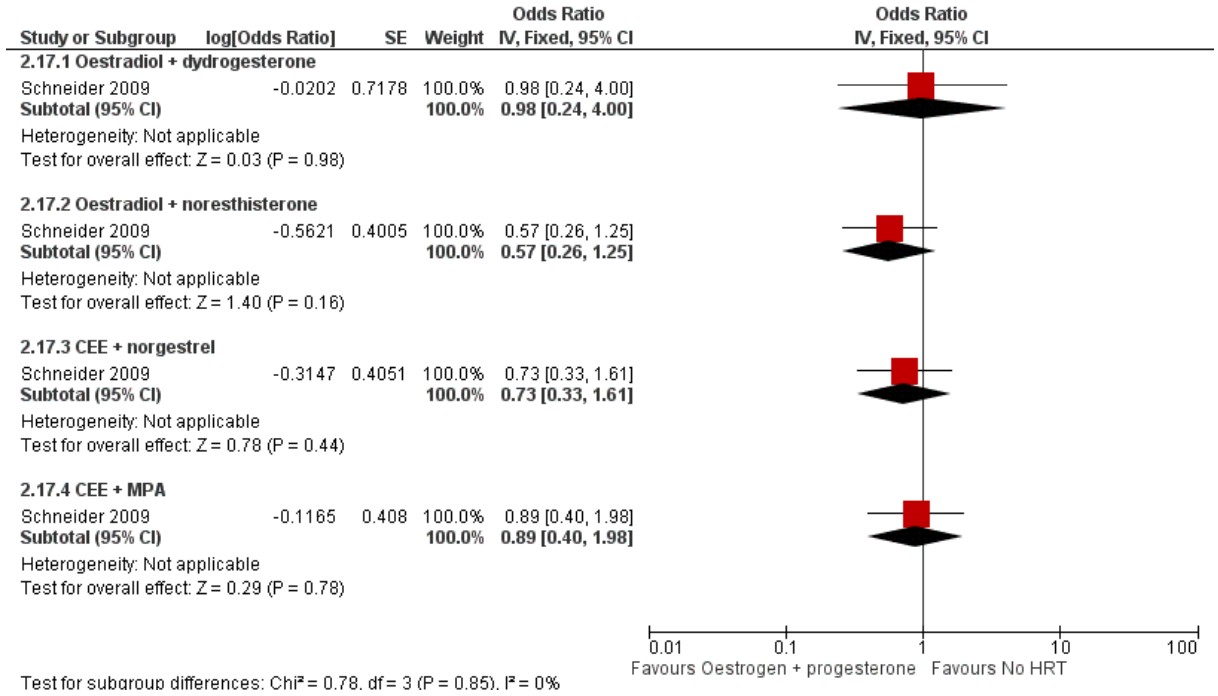


Figure 17: Incidence of endometrial cancer – current users, by BMI, any duration of use HR

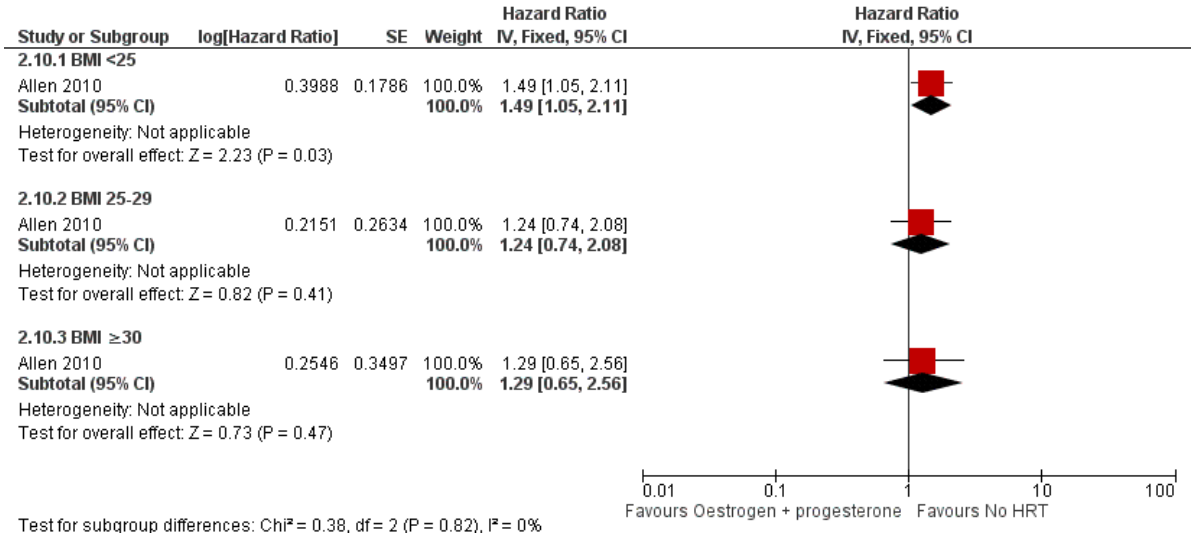
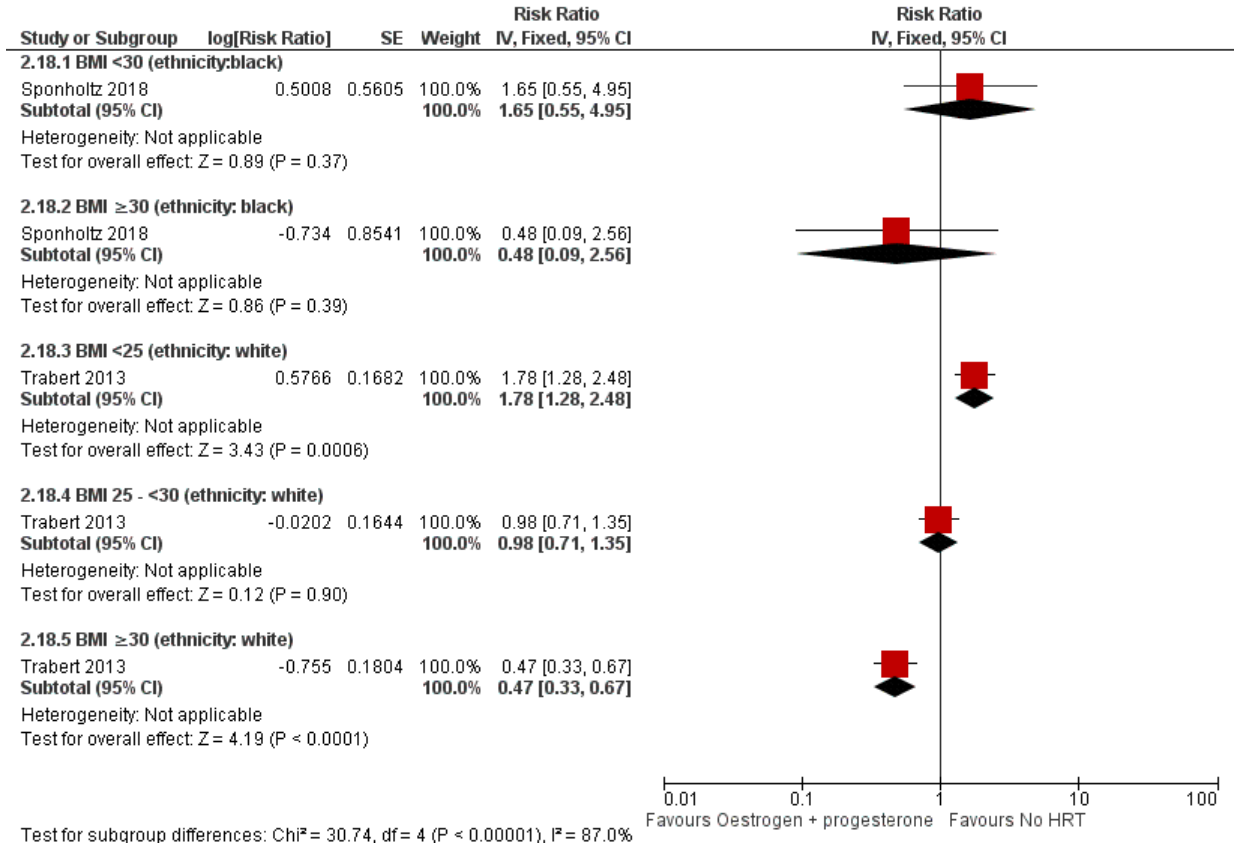
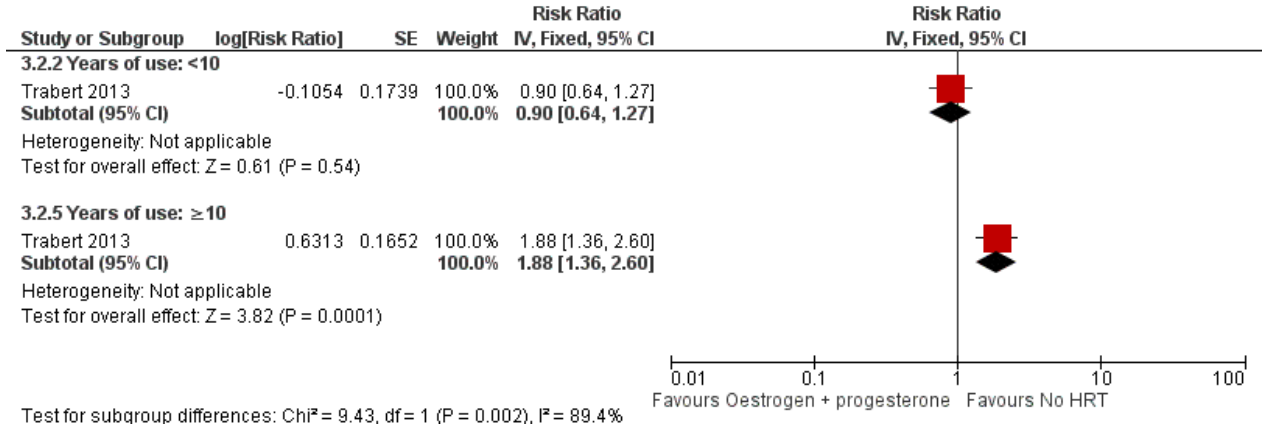


Figure 18: Incidence of endometrial cancer – current users, by BMI, any duration of use, RR (ethnicity)



Comparison 3: Sequential combined oestrogen and progestogen HRT versus no HRT

Figure 19: Incidence of endometrial cancer – current users, duration of use RR



Comparison 4: Continuous combined oestrogen and progestogen HRT versus no HRT

Figure 20: Incidence of endometrial cancer – all users, duration of use, RR

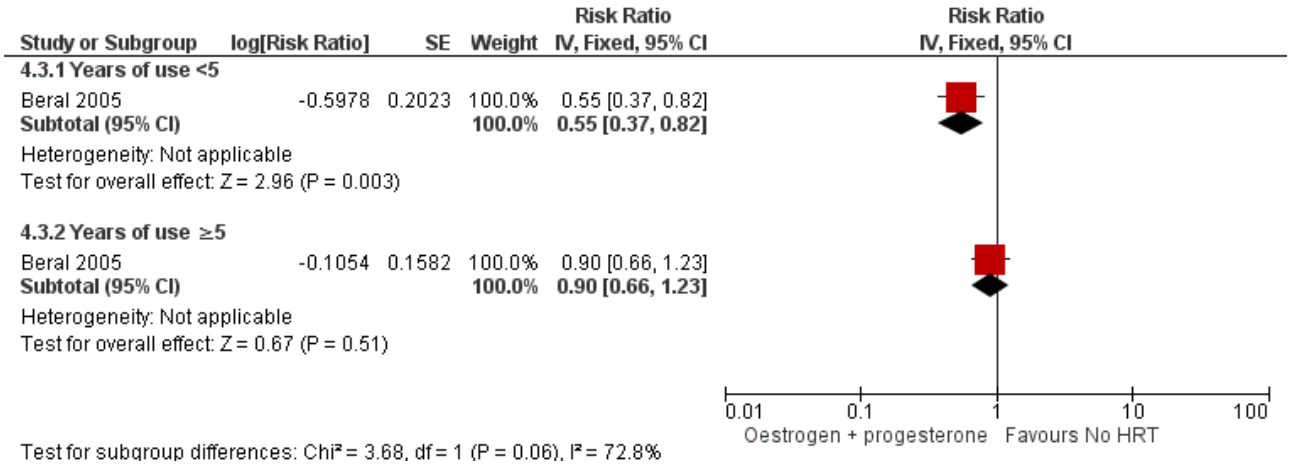


Figure 21: Incidence of endometrial cancer – all users, by constituent, any duration RR

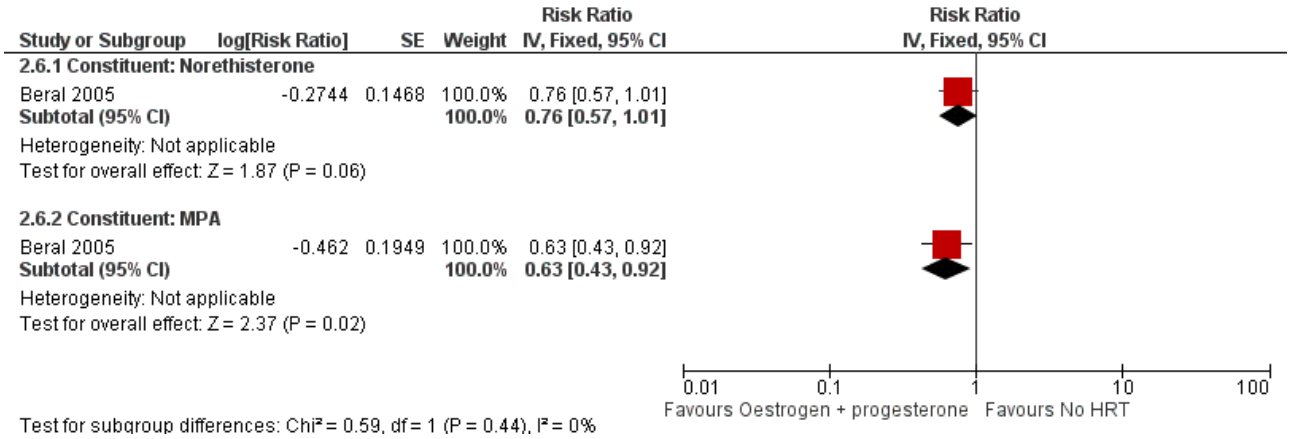


Figure 22: Incidence of endometrial cancer – current users, by route of administration, any duration RR

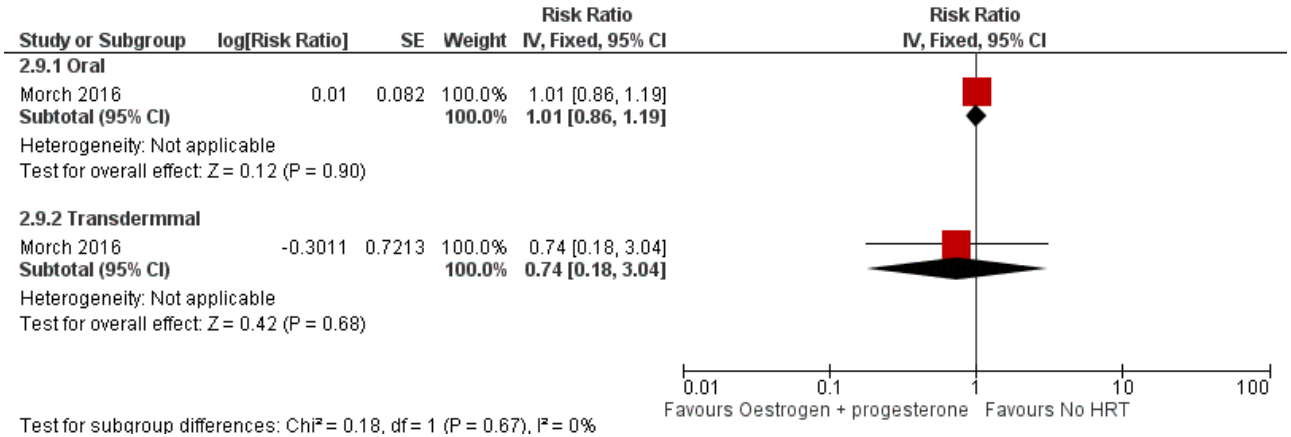
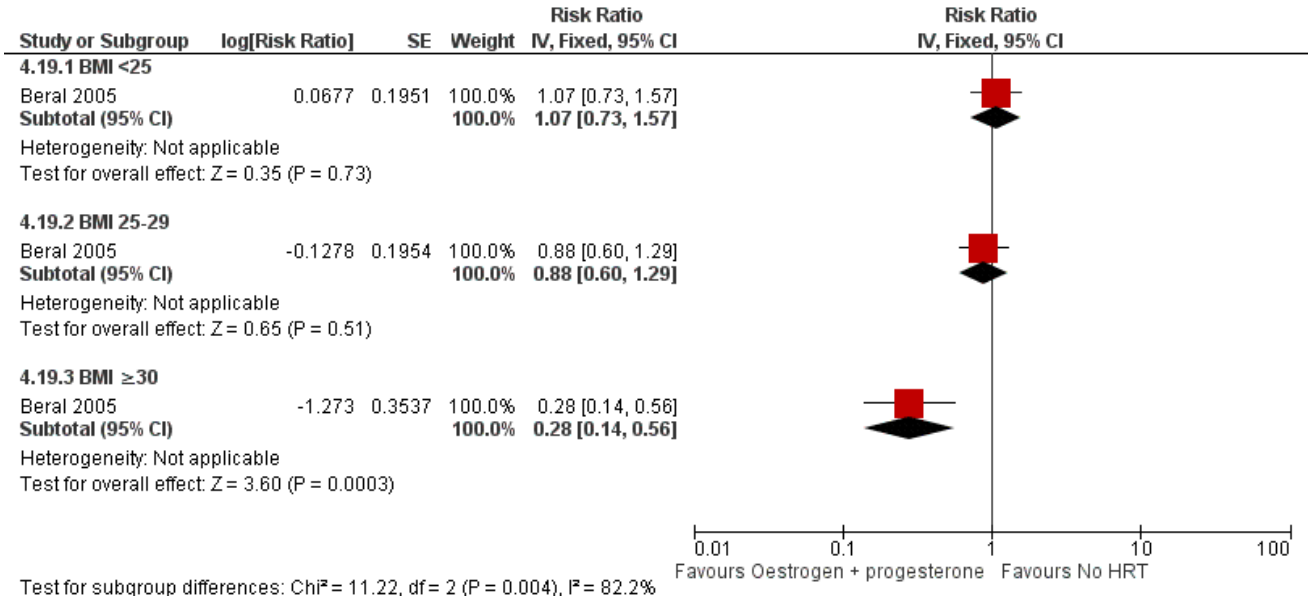


Figure 23: Incidence of endometrial cancer – all users, by BMI, any duration RR



Oestrogen-only HRT- randomised controlled trials forest plots

Comparison 5: Oestrogen-only HRT versus placebo

Figure 24: Current users, 1-4 years duration HRT: Incidence of endometrial cancer

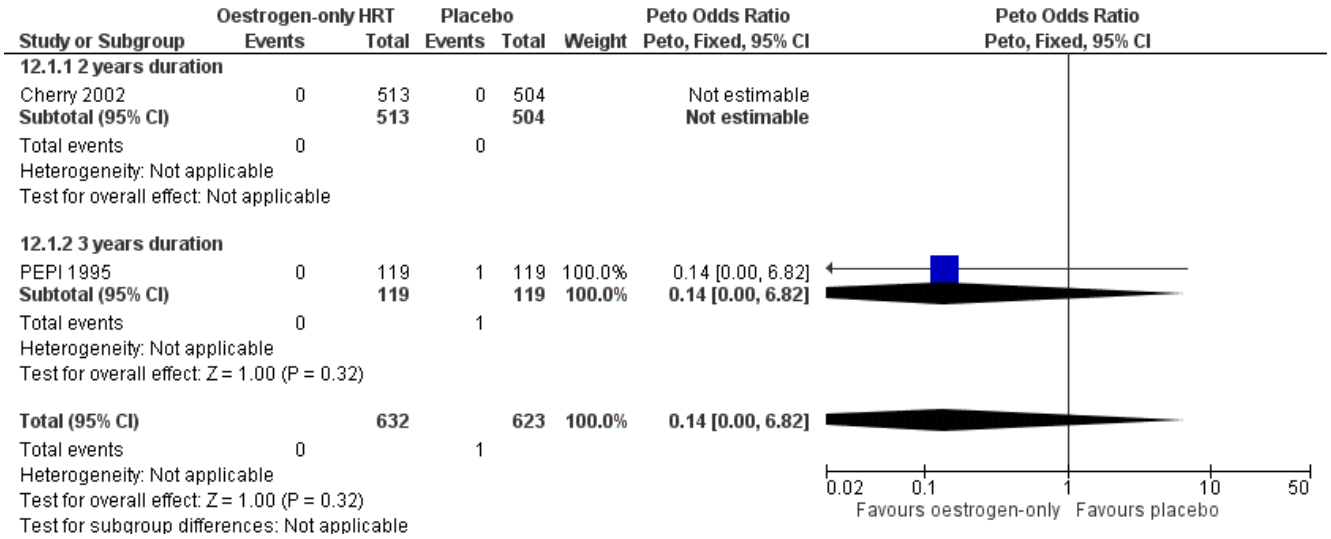
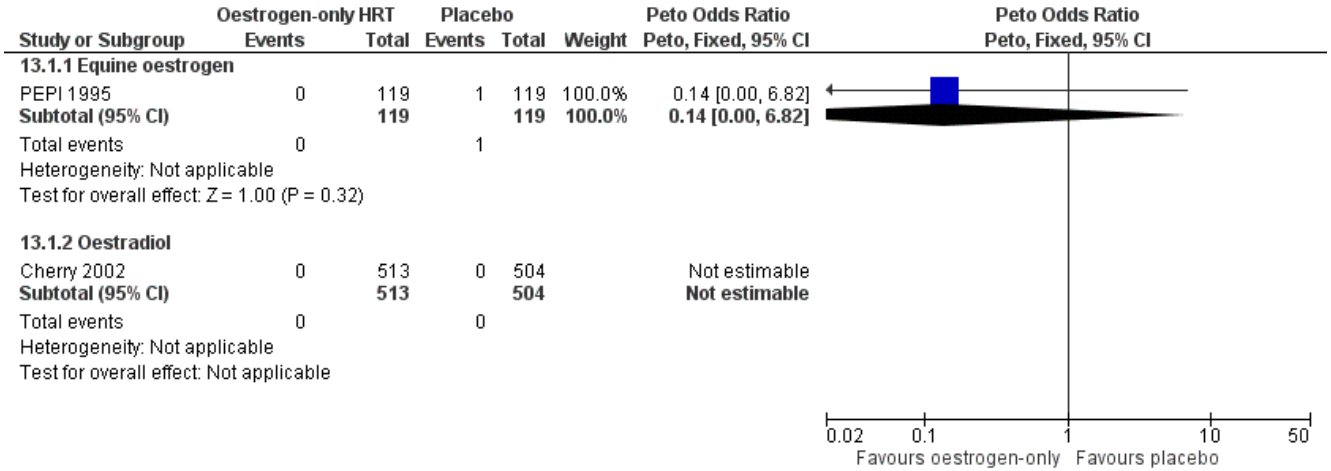


Figure 25: Current users, 1-4 years duration HRT by oestrogen constituent: Incidence of endometrial cancer



Oestrogen-only HRT- observational studies forest plots

Comparison 6: Oestrogen-only HRT versus no HRT

Figure 26: Incidence of endometrial cancer, current users, any duration of use, HR

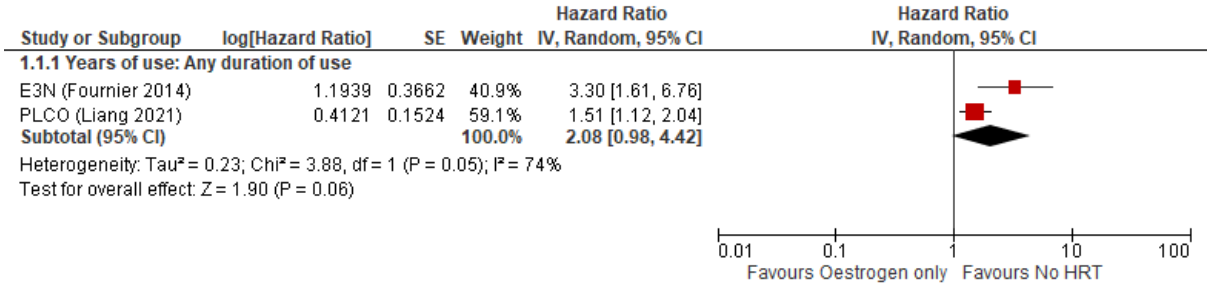


Figure 27: Incidence of endometrial cancer – current users, duration of use, RR

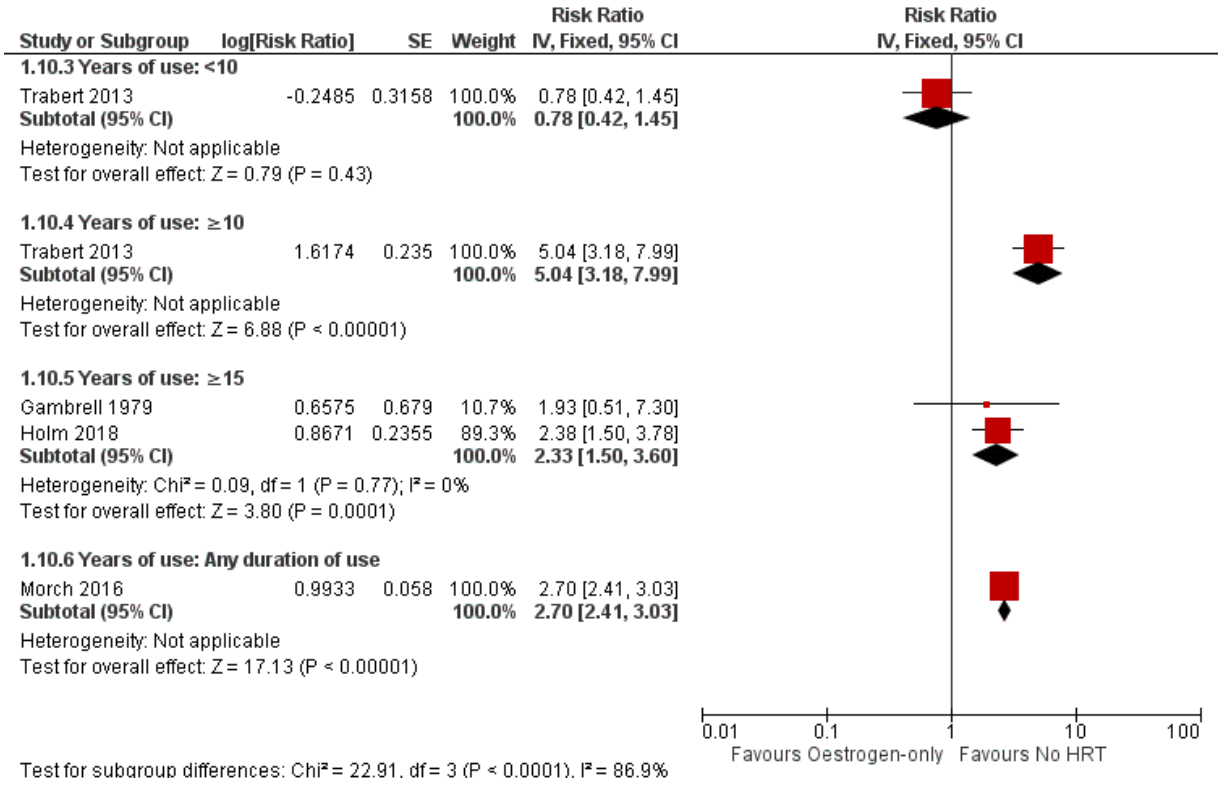


Figure 28: Incidence of endometrial cancer – all users, duration of use, HR

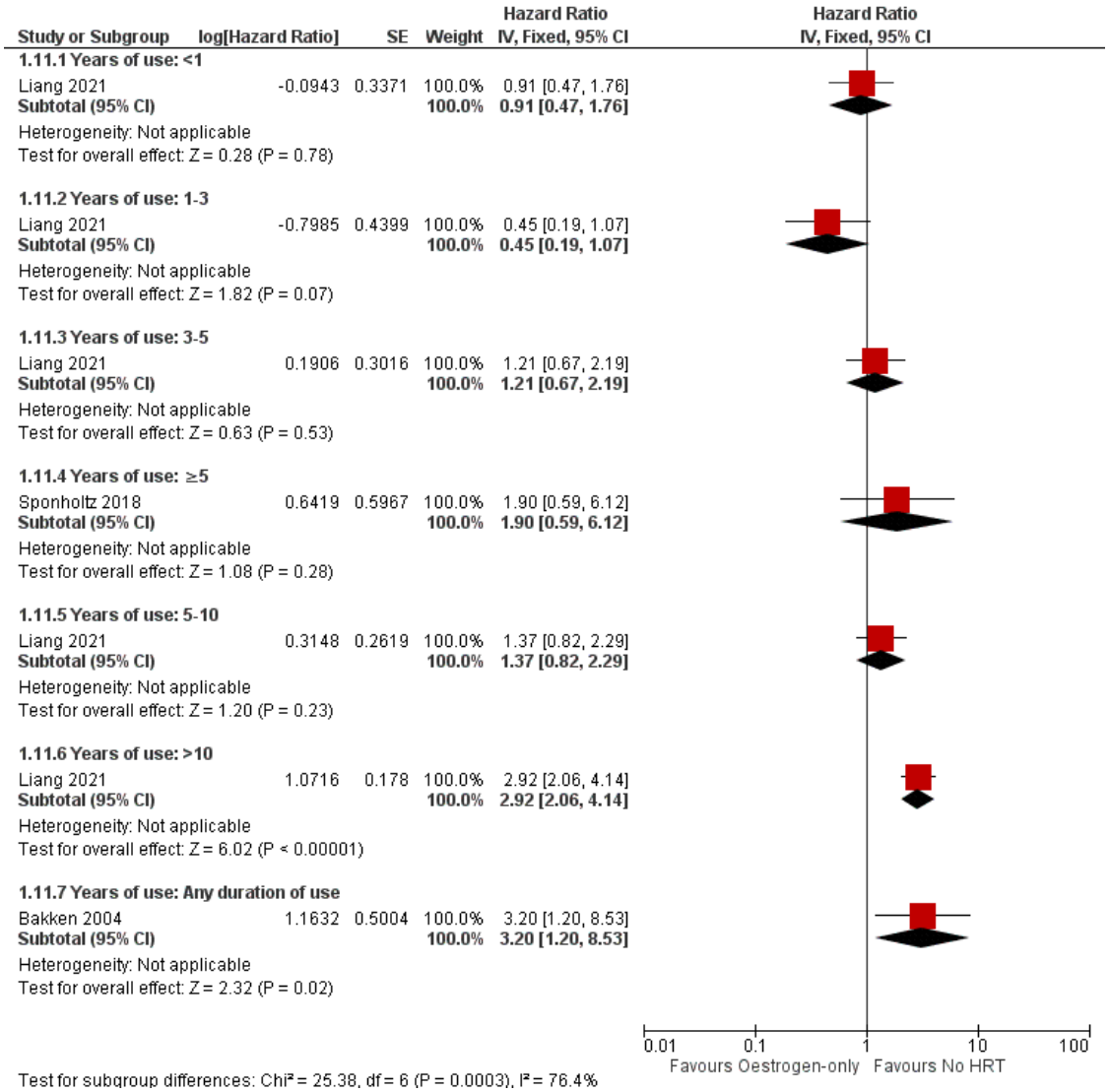


Figure 29: Incidence of endometrial cancer – current user, by constituent, any duration of use

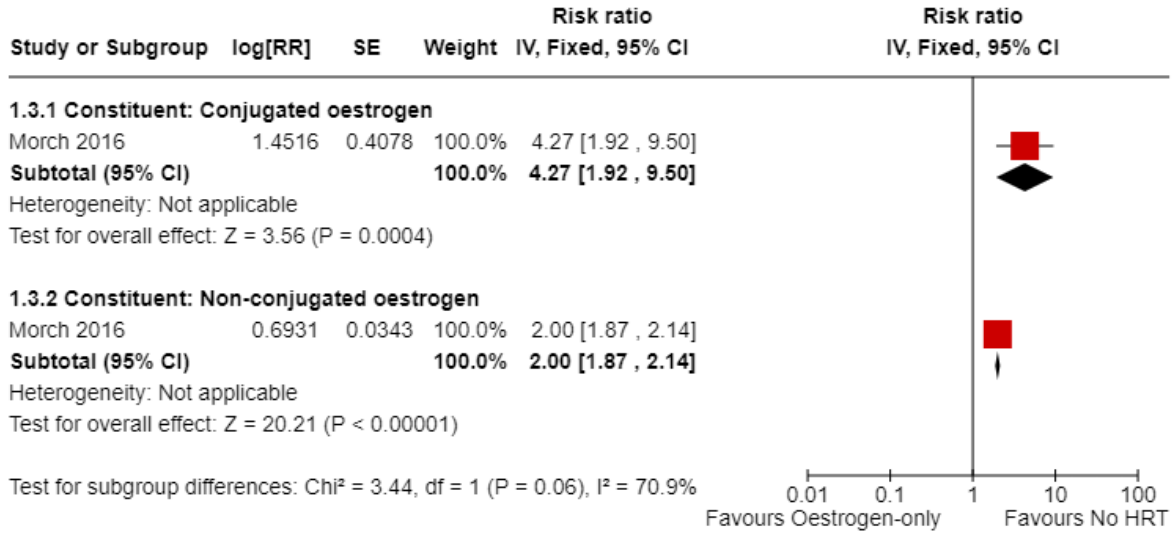


Figure 30: Incidence of endometrial cancer – current users, by route of administration, any duration of use HR

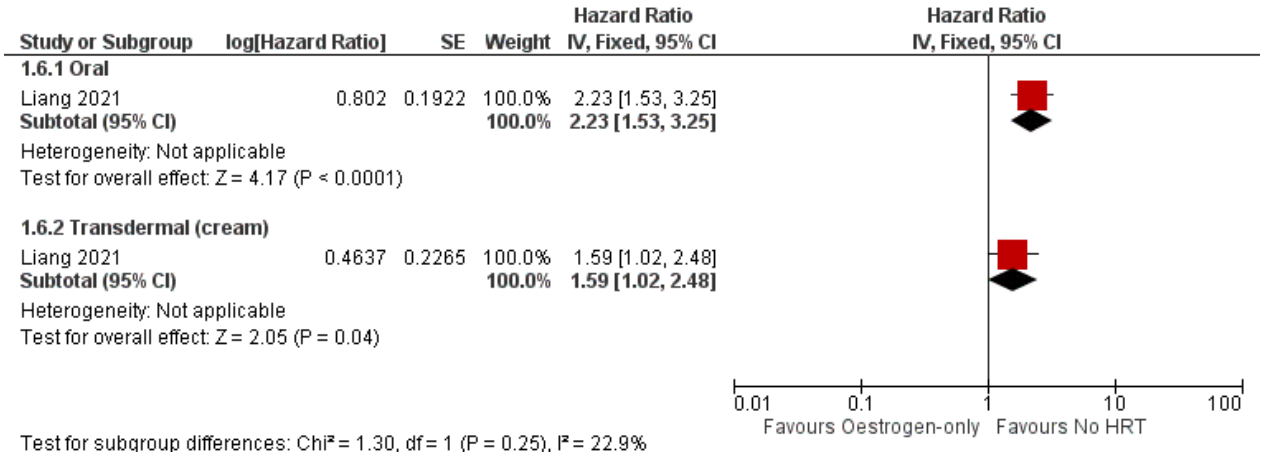


Figure 31: Incidence of endometrial cancer – current users, by route of administration, any duration of use RR

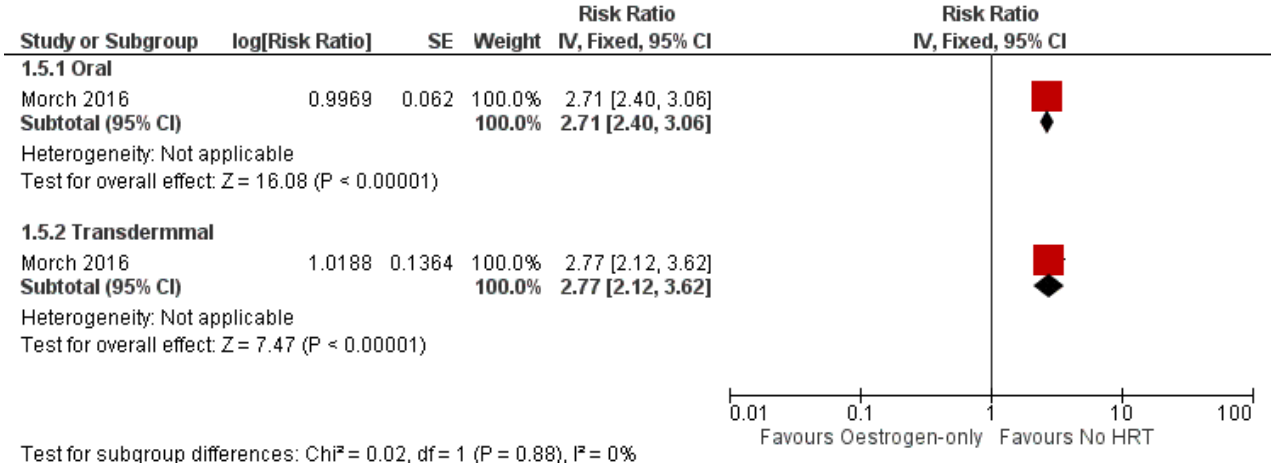


Figure 32: Incidence of endometrial cancer – current users, by BMI, any duration of use, HR

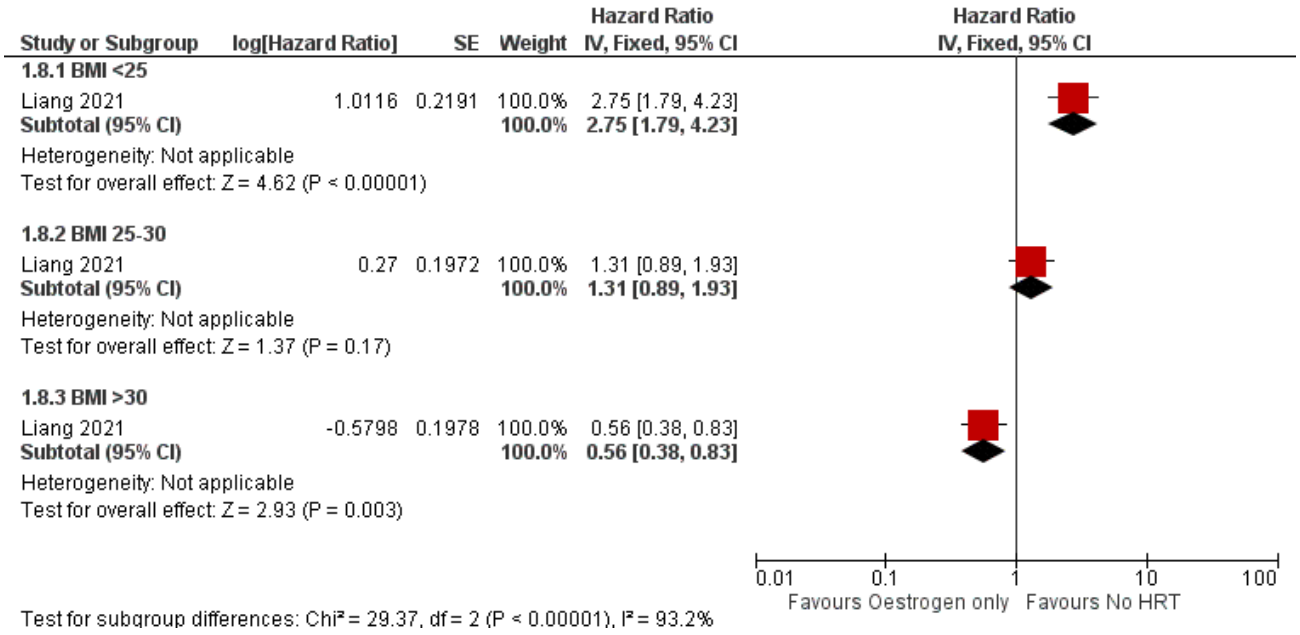
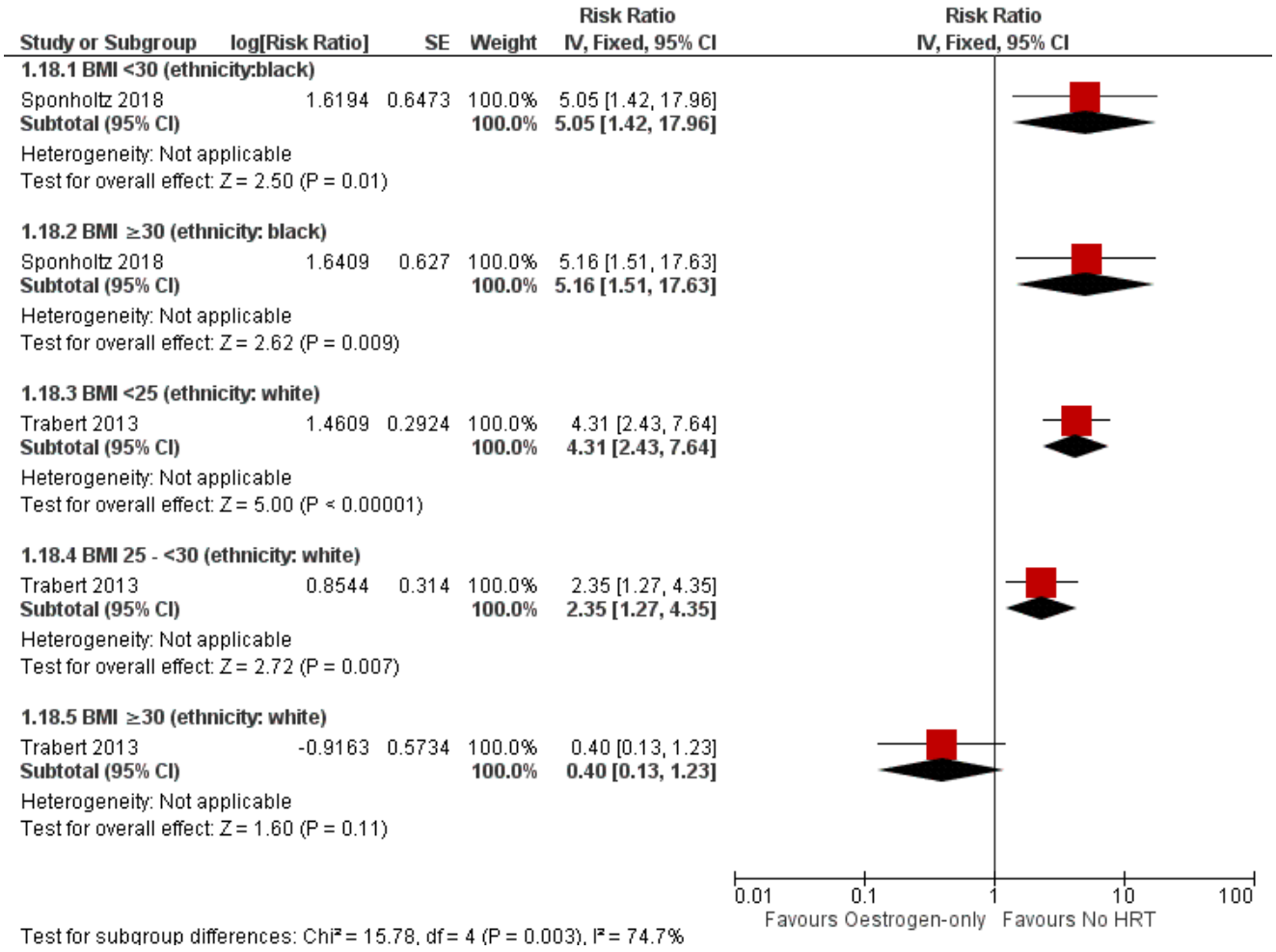


Figure 33: Incidence of endometrial cancer – current users, by BMI, any duration of use (ethnicity) RR



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 endometrial cancer?

See Appendix M for absolute risk tables relevant to the recommendations made.

Combined oestrogen + progestogen HRT- randomised controlled trials GRADE profiles

Comparison 1: Combined oestrogen and progestogen HRT versus placebo

Table 5: Current users, 1-4 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
1-4 years duration HRT - Incidence of EC (no. events)												
7[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	26/11068 (0.2%)	22/9998 (0.2%)	POR 1.00 (0.56 to 1.78)	0 fewer per 1000 (from 1 fewer to 2 more)	VERY LOW	CRITICAL
2 years duration HRT - Incidence of EC (no. events)												
3[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/588 (0.7%)	0/151 (0%)	POR 3.42 (0.25 to 47.49)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
3 years duration HRT - Incidence of EC (no. events)												
2[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/594 (0%)	2/362 (0.6%)	POR 0.06 (0.00 to 1.13)	5 fewer per 1000 (from 6 fewer to 1 more)	VERY LOW	CRITICAL
4 years duration HRT - Incidence of EC (no. events)												
2[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	22/9886 (0.2%)	20/9485 (0.2%)	POR 1.06 (0.58 to 1.93)	0 more per 1000 (from 1 fewer to 2 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio
[1] Byrjalsen 1999, Ferenczy 2002, Hulley 1998, Langer 2006, Obel 1993, PEPI 1995, Roussow 2002
[2]Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[3]95% CI crosses 2 MIDs
[4]Byrjalsen 1999, Ferenczy 2002, Obel 1993
[5]Langer 2006, PEPI 1995
[6]Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[7]Hulley 1998, Roussow 2002

Table 6: Current users, 1-4 years duration HRT by oestrogen constituent

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Equine Oestrogen - Incidence of EC (no. events)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	22/10480 (0.2%)	22/9847 (0.2%)	POR 0.94 (0.52 to 1.70)	0 fewer per 1000 (from 1 fewer to 2 more)	LOW	CRITICAL
Oestradiol - Incidence of EC (no. events)												
3[3]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/588 (0.7%)	0/151 (0%)	POR 3.42 (0.25 to 47.49)	0 more per 1000 (from - 0.00 to 0.00)	VERY LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio
[1]Hulley 1998, Langer 2008, PEPI 1995, Roussow 2002
[2]95% CI crosses 2 MIDs
[3]Byrjalsen 1999, Ferenczy 2002, Obel 1993
[4]Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 7: Current users, 1-4 years duration HRT by progestogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Medroxyprogesterone acetate (MPA) - Incidence of EC (no. events)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	22/10360 (0.2%)	22/9847 (0.2%)	POR 0.95 (0.52 to 1.71)	0 fewer per 1000 (from 1 fewer to 2 more)	LOW	CRITICAL
Micronized progesterone (MP) - Incidence of EC (no. events)												
1 (PEPI 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/120 (0%)	1/119 (0.8%)	POR 0.13 (0.00 to 6.76)	7 fewer per 1000 (from 8 fewer to 46 more)	LOW	CRITICAL
Norethisterone acetate (NETA) – Incidence of EC (no. events)												
1 (Obel 1993)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/84 (0%)	0/45 (0%)	RD 0.00 (-0.03 to 0.03)	0 more per 1000 (from - 0.00 to 0.00)	VERY LOW	CRITICAL
Any synthetic progestin - Incidence of EC (no. events)												
2[5]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/504 (0.8%)	0/106 (0%)	POR 3.42 (0.25 to 47.49)	0 more per 1000 (from - 0.00 to 0.00)	VERY LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio; RD: risk difference
[1]Hulley 1998, Langer 2008, PEPI 1995, Roussow 2002
[2]95% CI crosses 2 MIDs
[3]Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4]<150 events
[5]Byrjalsen 1999, Ferenczy 2002

Table 8: Current users, 1-4 years duration HRT with oestradiol by sequential dosage

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Oestradiol 2mg daily + 25ug gestodene days 17 to 28 - Incidence of EC (no. events)												
1 (Byrjalsen 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/27 (0%)	0/43 (0%)	RD 0.00 (-0.06 to 0.06)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 2mg daily + 50ug gestodene days 17 to 28 - Incidence of EC (no. events)												
1 (Byrjalsen 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0/43 (0%)	RD 0.00 (-0.05 to 0.05)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 2mg daily + dydrogesterone 20mg days 15 to 28 - Incidence of EC (no. events)												
1 (Ferenczy 2002)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/96 (2.1%)	0/63 (0%)	POR 5.3 (0.31 to 90.86)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 2mg daily + dydrogesterone 10mg days 15 to 28 - Incidence of EC (no. events)												
1 (Ferenczy 2002)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/88 (0%)	0/63 (0%)	RD 0.00 (-0.03 to 0.03)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 1mg daily + dydrogesterone 10mg days 15 to 28 - Incidence of EC (no. events)												
1 (Ferenczy 2002)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/95 (0%)	0/63 (0%)	RD 0.00 (-0.03 to 0.03)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 1mg daily + dydrogesterone 5mg days 15 to 28 – Incidence of EC (no. events) -												
1 (Ferenczy 2002)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/100 (1%)	0/63 (0%)	POR 5.1 (0.09 to 285.72)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 1mg daily + 25ug gestodene days 17 to 28 - Incidence of EC (no. events)												
1 (Byrjalsen 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/34 (0%)	0/43 (0%)	RD 0.00 (-0.05 to 0.05)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL
Oestradiol 2mg days 1 to 22 + 1mg NETA days 1 to 10 + Oestradiol 1mg days 23 to 28 - Incidence of EC (no. events)												
1 (Obel 1993)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/45 (0%)	0/45 (0%)	RD 0.00 (-0.04 to 0.04)	0 more per 1000 (from -0.00 to 0.00)	VERY LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; µg: micrograms; mg: milligrams; NETA: norethisterone acetate; POR: Peto odds ratio RD: risk difference;
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4] 95% CI crosses 2 MIDs

Table 9: Current users, 1-4 years duration HRT with equine oestrogen by sequential dosage

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
CEE 0.625mg daily + MPA 10mg days 1 to 12 - Incidence of EC (no. events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
1 (PEPI 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/118 (0%)	1/119 (0.8%)	POR 0.14 (0.00 to 6.88)	7 fewer per 1000 (from 8 fewer to 47 more)	LOW	CRITICAL
CEE 0.625mg daily + MP 200mg days 1 to 12 - Incidence of EC (no. events)												
1 (PEPI 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/120 (0%)	1/119 (0.8%)	POR 0.13 (0.00 to 6.76)	7 fewer per 1000 (from 8 fewer to 46 more)	LOW	CRITICAL

CEE: conjugated equine oestrogen; CI: confidence interval; EC: endometrial cancer; mg: milligrams; MP: micronized progesterone; MPA: medroxyprogesterone acetate; POR: Peto odds ratio

[1]95% CI crosses 2 MIDs

Table 10: Current users, 5-9 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
5-9 years duration HRT - Incidence of EC (no. events)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	29/9886 (0.3%)	35/9485 (0.4%)	RR 0.79 (0.49 to 1.3)	1 fewer per 1000 (from 2 fewer to 1 more)	LOW	CRITICAL
Mean 5.6 years duration HRT - Incidence of EC (no. events)												
1 (Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/8506 (0.3%)	30/8102 (0.4%)	RR 0.86 (0.51 to 1.44)	1 fewer per 1000 (from 2 fewer to 2 more)	LOW	CRITICAL
Mean 6.8 years duration HRT - Incidence of EC (no. events)												
1(Hulley 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/1380 (0.1%)	5/1383 (0.4%)	RR 0.4 (0.08 to 2.06)	2 fewer per 1000 (from 3 fewer to 4 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio

[1] Manson 2013, Hulley 2002

[2]95% CI crosses 2 MIDs

Table 11: Current users, 5-9 years duration HRT by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Age 50-59 years at first use - Incidence of EC (no. events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
1 (Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/2837 (0.2%)	5/2683 (0.2%)	RR 1.13 (0.35 to 3.71)	0 more per 1000 (from 1 fewer to 5 more)	LOW	CRITICAL
Age 60-69 years at first use - Incidence of EC (no. events)												
1 (Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/3854 (0.4%)	17/3655 (0.5%)	RR 0.78 (0.39 to 1.58)	1 fewer per 1000 (from 3 fewer to 3 more)	LOW	CRITICAL
Age >69 years at first use - Incidence of EC (no. events)												
1 (Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/1815 (0.4%)	8/1764 (0.5%)	RR 0.85 (0.31 to 2.34)	1 fewer per 1000 (from 3 fewer to 6 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 2 MIDs

Table 12: Current and past users (of variable recency), 5-9 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Cumulative follow-up 8.5 years - Incidence of EC (no. events)												
1 (Heiss 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	44/8506 (0.5%)	52/8102 (0.6%)	RR 0.81 (0.54 to 1.2)	1 fewer per 1000 (from 3 fewer to 1 more)	MODERATE	CRITICAL
Cumulative follow-up median 13.2 years- Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	66/8506 (0.8%)	95/8102 (1.2%)	RR 0.66 (0.48 to 0.90)	4 fewer per 1000 (from 1 fewer to 6 fewer)	MODERATE	CRITICAL
Cumulative follow-up median 18 years - Incidence of EC (no. events)												
1 (Prentice 2021)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	97/8506 (1.1%)	127/8102 (1.6%)	RR 0.73 (0.56 to 0.95)	4 fewer per 1000 (from 1 fewer to 7 fewer)	MODERATE	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 1 MID

Table 13: Current and past users (variable recency), 5-9 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Current and past users (variable recency), 5-9 years duration HRT, Mortality from EC												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/8506 (0.06%)	11/8102 (0.14%)	RR 0.43 (0.15 to 1.25)	1 fewer per 1000 (from 1 fewer to 0 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; HRT: hormone replacement therapy; RR: risk ratio

[1] <150 events

Table 14: Current and past users, 5-9 years duration HRT by age at first use at 13.2 years follow-up

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
Age 50-59 years at first use - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	22/2266 (1%)	31/2128 (1.5%)	RR 0.67 (0.39 to 1.15)	5 fewer per 1000 (from 9 fewer to 2 more)	MODERATE	CRITICAL
Age 60-69 years at first use - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31/3019 (1%)	43/2887 (1.5%)	RR 0.69 (0.44 to 1.09)	5 fewer per 1000 (from 8 fewer to 1 more)	MODERATE	CRITICAL
Age >69 years at first use - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13/1260 (1%)	21/1228 (1.7%)	RR 0.60 (0.30 to 1.2)	7 fewer per 1000 (from 12 fewer to 3 more)	MODERATE	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 1 MID

Table 15: Current and past users, 5-9 years duration HRT by ethnicity at 13.2 years follow-up

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
White - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	60/5616 (1.1%)	78/5317 (1.5%)	RR 0.73 (0.52 to 1.02)	4 fewer per 1000 (from 7 fewer to 0 more)	MODERATE	CRITICAL
Black - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/406 (0.7%)	9/401 (2.2%)	RR 0.33 (0.09 to 1.21)	15 fewer per 1000 (from 20 fewer to 5 more)	MODERATE	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 1 MID

Table 16: Current and past users, 5-9 years duration HRT by BMI at 13.2 years follow-up

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT	Control	Relative (95% CI)	Absolute		
BMI <25 - Incidence of EC (no. events)												

1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	9/1998 (0.5%)	11/1949 (0.6%)	RR 0.80 (0.33 to 1.92)	1 fewer per 1000 (from 4 fewer to 5 more)	LOW	CRITICAL
BMI ≥25 - Incidence of EC (no. events)												
1 (Chlebowski 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/4518 (1.3%)	94/4253 (2.2%)	RR 0.57 (0.41 to 0.79)	10 fewer per 1000 (from 5 fewer to 13 fewer)	HIGH	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 2 MIDs

Table 17: Current users, 10-14 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined: Current users, 10-14 years duration HRT**	**Control**	**Relative (95% CI)**	**Absolute**		
10-14 years duration HRT - Incidence of EC (no. events)												
1 (Nachtigall 1979)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/84 (0%)	1/84 (1.2%)	POR 0.14 (0.00 to 6.82)	10 fewer per 1000 (from 12 fewer to 64 more)	VERY LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio
Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[1]95% CI crosses 2 MIDs

Table 18: Recency <5 years since last use, 5-9 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT**	**Control**	**Relative (95% CI)**	**Absolute**		
5-9 years duration HRT - Incidence of EC (no. events)												
1 (Heiss 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17/8052 (0.2%)	21/7678 (0.3%)	RR 0.77 (0.41 to 1.46)	1 fewer per 1000 (from 2 fewer to 1 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 2 MIDs

Combined oestrogen + progestogen HRT- observational studies GRADE profiles

Comparison 2: Any combined oestrogen and progestogen HRT versus no HRT

Table 19: Oestrogen + progestogen HRT versus no HRT for incidence of endometrial cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen HRT	No HRT	Relative (95% CI)	Absolute		
Incidence of endometrial cancer- current users, duration of use, HR - Years of use: <2												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 1.46 (0.94 to 2.27)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, duration of use, HR - Years of use: >2												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 1.64 (1.11 to 2.42)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, duration of use, HR - Years of use: Any duration of use												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 0.93 (0.72 to 1.2)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: 1-4												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	NR		RR 0.79 (0.47 to 1.33)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥5												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	NR		RR 0.99 (0.49 to 2)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: <10												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		RR 1.3 (0.54 to 3.13)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥10												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		RR 1.44 (1.11 to 1.87)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥15												
2[4]	cohort study	no serious risk of bias	serious[5]	no serious indirectness	very serious[2]	none	NR		RR 0.9 (0.14 to 5.63)	See Appendix M	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen HRT	No HRT	Relative (95% CI)	Absolute		
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: <1												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 1.2 (0.83 to 1.73)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 1-3												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 1.04 (0.71 to 1.52)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 3-5												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 0.69 (0.41 to 1.16)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 5-10												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 1 (0.65 to 1.54)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: >10 years												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 0.59 (0.3 to 1.16)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: Any duration of use												
1 (Bakken 2004)	cohort study	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 0.7 (0.4 to 1.22)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration of use, HR - Constituent: Micronized progesterone												
1 (Fournier 2014)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		HR 1.96 (1.41 to 2.72)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration of use, HR - Constituent: Dydrogesterone												
1 (Fournier 2014)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 0.67 (0.36 to 1.25)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration of use, HR - Constituent: Other progesterone derivative												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen HRT	No HRT	Relative (95% CI)	Absolute		
1 (Fournier 2014)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 0.65 (0.41 to 1.03)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration, OR - Oestradiol + dydrogesterone												
1 (Schneider 2009)	case control	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		OR 0.98 (0.24 to 4)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration, OR - Oestradiol + norethisterone												
1 (Schneider 2009)	case control	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		OR 0.57 (0.26 to 1.25)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration, OR - CEE + norgestrel												
1 (Schneider 2009)	case control	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		OR 0.73 (0.33 to 1.61)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration, OR - CEE + MPA												
1 (Schneider 2009)	case control	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		OR 0.89 (0.4 to 1.98)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI <25												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 1.49 (1.05 to 2.11)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI 25-29												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 1.24 (0.74 to 2.08)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI ≥30												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		HR 1.29 (0.65 to 2.56)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: black) - BMI <30												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	NR		RR 1.65 (0.55 to 4.95)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: black) - BMI ≥30												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	NR		RR 0.48 (0.09 to 2.56)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI <25												
						none	NR			-	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen HRT	No HRT	Relative (95% CI)	Absolute		
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision				RR 1.78 (1.28 to 2.48)			
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI 25-<30												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		RR 0.98 (0.71 to 1.35)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI ≥30												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 0.47 (0.33 to 0.67)	-	HIGH	CRITICAL

BMI: body mass index; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy, NR: not reported; OR: odds ratio; RR: risk ratio
**Study reported IRR which has been analysed as RR*
[1] 95% CI crosses 1 MID
[2] 95% CI crosses 2 MIDs
[3] Serious indirectness due to population including women ≥40 years
[4] Gambrell 1979, Holm 2018
[5] Serious heterogeneity unexplained by subgroup analysis
[6] Serious risk of bias in the evidence contributing to outcomes as per ROBINS-I

Comparison 3: Sequential combined oestrogen and progestogen HRT versus no HRT

Table 20: Oestrogen + progesterone HRT versus no HRT- Sequential for incidence of endometrial cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential combined oestrogen + progesterone HRT	No HRT	Relative (95% CI)	Absolute		
Incidence of endometrial cancer- current users, duration of use, HR - Years of use: Any duration of use (progestin use 10-14 days per month)												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		HR 1.52 (1 to 2.31)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: <10 (progestin use less than 15 days per month)												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	NR		RR 0.9 (0.64 to 1.27)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥10 (progestin use less than 15 days per month)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential combined oestrogen + progesterone HRT	No HRT	Relative (95% CI)	Absolute		
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 1.88 (1.36 to 2.6)	See Appendix M	HIGH	CRITICAL

BMI: body mass index; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy, NR: not reported; RR: risk ratio
[1] 95% CI crosses 1 MID
[2] 95% CI crosses 2 MIDs

Comparison 4: Continuous combined oestrogen and progestogen HRT versus no HRT

Table 21: Oestrogen + progesterone HRT versus no HRT- Continuous for incidence of endometrial cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progesterone HRT	No HRT	Relative (95% CI)	Absolute		
Incidence of endometrial cancer- current users, duration of use, HR - Years of use: Any duration of use												
1 (Allen 2010)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		HR 0.24 (0.08 to 0.72)	See Appendix M	HIGH	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: Any duration of use												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	NR		RR 1.02 (0.87 to 1.2)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, duration of use, RR - Years of use: <5												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR		RR 0.55 (0.37 to 0.82)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, RR - Years of use: ≥5												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR		RR 0.9 (0.66 to 1.23)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration, RR - Constituent: Norethisterone												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 1.01 (0.86 to 1.19)	-	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progesterone HRT	No HRT	Relative (95% CI)	Absolute		
Incidence of endometrial cancer- all users, by constituent, any duration, RR - Constituent: Norethisterone												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR		RR 0.76 (0.57 to 1.01)	-	LOW	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration, RR - Constituent: MPA												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR		RR 0.63 (0.43 to 0.92)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration, RR - Oral												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 1.01 (0.86 to 1.19)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration, RR - Transdermal												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	NR		RR 0.74 (0.18 to 3.04)	-	LOW	CRITICAL
Incidence of endometrial cancer- all users, by BMI, any duration, RR - BMI <25												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR		RR 1.07 (0.73 to 1.57)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, by BMI, any duration, RR - BMI 25-29												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR		RR 0.88 (0.6 to 1.29)	-	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, by BMI, any duration, RR - BMI ≥30												
1 (Beral 2005)	cohort study	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 0.28 (0.14 to 0.56)	-	MODERATE	CRITICAL

BMI: body mass index; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy, NR: not reported; RR: risk ratio
[1] 95% CI crosses 1 MID
[2] Serious risk of bias in the evidence contributing to outcomes as per ROBINS-I
[3] 95% CI crosses 2 MIDs

Oestrogen-only HRT- randomised controlled trials GRADE profiles

Comparison 5: Oestrogen-only versus placebo

Table 22: Current users, 1-4 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	Control	Relative (95% CI)	Absolute		
1-4 years duration HRT - Incidence of EC (no. events)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/632 (0%)	1/623 (0.2%)	POR 0.14 (0.00 to 6.82)	1 fewer per 1000 (from 2 fewer to 9 more)	LOW	CRITICAL
2 years duration HRT – Incidence of EC (no. events)												
1 (Cherry 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/513 (0%)	0/504 (0%)	RD 0.00 (-0.00 to 0.00)	0 fewer per 1000 (from 0 to 0)	LOW	CRITICAL
3 years duration HRT - Incidence of EC (no. events)												
1 (PEPI 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/119 (0%)	1/119 (0.8%)	POR 0.14 (0.00 to 6.82)	7 fewer per 1000 (from 8 fewer to 46 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio
[1]Cherry 2002, PEPI 1995
[2]95% CI crosses 2 MIDs
[3]<150 events

Table 23: Current users, 1-4 years duration HRT by oestrogen constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	Control	Relative (95% CI)	Absolute		
Equine oestrogen - Incidence of EC (no. events)												
1 (PEPI 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/119 (0%)	1/119 (0.8%)	POR 0.14 (0 to 6.82)	7 fewer per 1000 (from 8 fewer to 46 more)	LOW	CRITICAL
Oestradiol - Incidence of EC (no. events)												
1 (Cherry 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/513 (0%)	0/504 (0%)	RD 0.00 (-0.00 to 0.00)	0 fewer per 1000 (from 0 to 0)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; POR: Peto odds ratio; RD: risk difference
[1]95% CI crosses 2 MIDs
[2]<150 events

Table 24: Recency 10-14 years since last use, 1-4 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	Control	Relative (95% CI)	Absolute		
Recency 10-14 years since last use, 1-4 years duration HRT - Incidence of EC (no. events)												

1 (Cherry 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/513 (0.2%)	2/504 (0.4%)	RR 0.49 (0.04 to 5.4)	2 fewer per 1000 (from 4 fewer to 17 more)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; RR: risk ratio
[1]95% CI crosses 2 MIDs

Table 25: Recency 10-14 years since last use, 1-4 years duration HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	Control	Relative (95% CI)	Absolute		
Recency 10-14 years since last use, 1-4 years duration HRT - Mortality from EC												
1 (Cherry 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/513 (0%)	0/504 (0%)	RD 0.00 (-0.00 to 0.00)	0 fewer per 1000 (from 0 to 0)	LOW	CRITICAL

CI: confidence interval; EC: endometrial cancer; HRT: hormone replacement therapy; RD: risk difference
[1] <150 events

Oestrogen-only HRT - observational studies GRADE profiles

Comparison 6: Oestrogen-only versus no HRT

Table 26: Oestrogen-only versus no HRT for incidence of endometrial cancer

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 endometrial cancer- current users, duration of use, HR - Years of use: Any duration of use												
2[1]	cohort study	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	NR		HR 2.08 (0.98 to 4.42)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: <10												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR		RR 0.78 (0.42 to 1.45)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥10												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 5.04 (3.18 to 7.99)	See Appendix M	HIGH	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: ≥15												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
2[5]	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2.33 (1.5 to 3.6)	See Appendix M	HIGH	CRITICAL
Incidence of endometrial cancer- current users, duration of use, RR - Years of use: Any duration of use												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2.7 (2.41 to 3.03)	See Appendix M	HIGH	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: <1												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR		HR 0.91 (0.47 to 1.76)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 1-3												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 0.45 (0.19 to 1.07)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 3-5												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR		HR 1.21 (0.67 to 2.19)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: ≥5												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[6]	very serious[4]	none	NR		HR 1.9 (0.59 to 6.12)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: 5-10												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 1.37 (0.82 to 2.29)	See Appendix M	MODERATE	CRITICAL
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: >10 years												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		HR 2.92 (2.06 to 4.14)	See Appendix M	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		
Incidence of endometrial cancer- all users, duration of use, HR - Years of use: Any duration of use												
1 (Bakken 2004)	cohort study	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 3.2 (1.2 to 8.53)	See Appendix M	LOW	CRITICAL
Incidence of endometrial cancer- all users, duration of use, RR - Years of use: 1-4												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[6]	very serious[4]	none	NR		RR 1.25 (0.70 to 2.23)	See Appendix M	VERY LOW	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration of use - Constituent: Conjugated oestrogen												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 4.27 (1.92 to 9.5)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by constituent, any duration of use - Constituent: Non-conjugated oestrogen												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2 (1.87 to 2.14)	-	HIGH	CRITICAL
Incidence of endometrial cancer- all users, by constituent, any duration of use - Constituent: Oestriol												
1 (Bakken 2004)	cohort study	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 3.1 (1.2 to 8.01)	-	LOW	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration of use, HR - Oral												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		HR 2.23 (1.53 to 3.25)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration of use, HR - Transdermal (cream)												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 1.59 (1.02 to 2.48)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration of use, RR - Oral												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2.71 (2.4 to 3.06)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by route of administration, any duration of use, RR - Transdermal												
1 (Morch 2016)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2.77 (2.12 to 3.62)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI <25												
1 (Liang 2021)						none	NR			-	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		
	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision				HR 2.75 (1.79 to 4.23)			
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI 25-30												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 1.31 (0.89 to 1.93)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, HR - BMI >30												
1 (Liang 2021)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	NR		HR 0.56 (0.38 to 0.83)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: black) - BMI <30												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	NR		RR 5.05 (1.42 to 17.96)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: black) - BMI ≥30												
1 (Sponholtz 2018)*	cohort study	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	NR		RR 5.16 (1.51 to 17.63)	-	MODERATE	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI <25												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 4.31 (2.43 to 7.64)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI 25-<30												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 2.35 (1.27 to 4.35)	-	HIGH	CRITICAL
Incidence of endometrial cancer- current users, by BMI, any duration of use, RR (ethnicity: white) - BMI ≥30												
1 (Trabert 2013)	cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR		RR 0.40 (0.13 to 1.26)	-	HIGH	CRITICAL

BMI: body mass index; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy, NR: not reported; RR: risk ratio
**Study reported IRR which has been analysed as RR*
[1] Fournier 2014, Liang 2021
[2] Serious heterogeneity unexplained by subgroup analysis
[3] 95% CI crosses 1 MID
[4] 95% CI crosses 2 MIDs
[5] Gambrell 1979, Holm 2018
[6] Serious indirectness due to population including women ≥40 years
[7] Serious risk of bias in the evidence contributing to outcomes as per ROBINS-I

Appendix G Economic evidence study selection

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

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

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 endometrial 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 endometrial 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 endometrial cancer?

Excluded effectiveness studies

Table 27: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Adami, H O, Persson, I, Hoover, R et al. (1989) Risk of cancer in women receiving hormone replacement therapy. International journal of cancer 44(5): 833-9	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Anderson, Garnet L, Judd, Howard L, Kaunitz, Andrew M et al. (2003) Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 290(13): 1739-48	Cohort already included (Manson 2013)
Antunes, C M, Strolley, P D, Rosenshein, N B et al. (1979) Endometrial cancer and estrogen use. Report of a large case-control study. The New England journal of medicine 300(1): 9-13	Study design - not a systematic review, randomised controlled trial, or observational study
Baik, S.H.; Baye, F.; McDonald, C.J. (2022) Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 7 million menopausal women over age 65: a retrospective observational study. medRxiv	Comparison - not placebo or no HRT
Beresford, S A, Weiss, N S, Voigt, L F et al. (1997) Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet (London, England) 349(9050): 458-61	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Bergkvist, L, Persson, I, Adami, H O et al. (1988) Risk factors for breast and endometrial cancer in a cohort of women treated with menopausal oestrogens. International journal of epidemiology 17(4): 732-7	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Bhupathiraju, Shilpa N, Grodstein, Francine, Rosner, Bernard A et al. (2017) Hormone Therapy Use and Risk of Chronic Disease in the Nurses' Health Study: A Comparative Analysis With the Women's Health Initiative. American journal of epidemiology 186(6): 696-708	Outcomes - reported outcomes do not match the review protocols
Bracco Suarez, Maria Beatriz, Benetti-Pinto, Cristina Laguna, Gibran, Luciano et al. (2021) Asymptomatic postmenopausal women: what are the risk factors for endometrial malignancies? A multicentric retrospective study. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 37(9): 853-856	Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen: unclear which HRT was given to women in this study

Study	Reason for exclusion
Brinton, L A and Hoover, R N (1993) Estrogen replacement therapy and endometrial cancer risk: unresolved issues. The Endometrial Cancer Collaborative Group. Obstetrics and gynecology 81(2): 265-71	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Brinton, L.A.; Lacey Jr., J.V.; Trimble, E.L. (2005) Hormones and endometrial cancer - New data from the Million Women Study. Lancet 365(9470): 1517-1518	Study design - not a systematic review, randomised controlled trial, or observational study
Canchola, Alison J, Chang, Ellen T, Bernstein, Leslie et al. (2010) Body size and the risk of endometrial cancer by hormone therapy use in postmenopausal women in the California Teachers Study cohort. Cancer causes & control: CCC 21(9): 1407-16	Outcomes - reported outcomes do not match the review protocols
Chang, Shih-Chen, Lacey, James V Jr, Brinton, Louise A et al. (2007) Lifetime weight history and endometrial cancer risk by type of menopausal hormone use in the NIH-AARP diet and health study. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 16(4): 723-30	Outcomes - reported outcomes do not match the review protocols
Crosbie, Emma J, Zwahlen, Marcel, Kitchener, Henry C et al. (2010) Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 19(12): 3119-30	Outcomes - reported outcomes do not match the review protocols.
Cushing, K L, Weiss, N S, Voigt, L F et al. (1998) Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. Obstetrics and gynecology 91(1): 35-9	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Di Donato, V., Palaia, I., D'Aniello, D. et al. (2020) Does Hormone Replacement Therapy Impact the Prognosis in Endometrial Cancer Survivors? A Systematic Review. Oncology (Switzerland) 98(4): 195-201	Systematic Review – reported outcomes do not match the review protocols (recurrence) and data on HRT use not collected at time of prescription or before the outcome was known for some studies. Relevant references checked for studies for inclusion
Doherty, Jennifer A, Cushing-Haugen, Kara L, Saltzman, Babette S et al. (2007) Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. American journal of obstetrics and gynecology 197(2): 139e1-7	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Edey, Katharine A; Rundle, Stuart; Hickey, Martha (2018) Hormone replacement therapy for women previously treated for endometrial cancer. The Cochrane database of systematic reviews 5: cd008830	Outcomes - reported outcomes do not match the review protocols
Epstein, Elisabeth; Lindqvist, Pelle G; Olsson, Hakan (2009) A population-based cohort study on the use of hormone treatment and	Outcomes - reported outcomes do not match the review protocols: ever and never users only (recency unclear)

Study	Reason for exclusion
endometrial cancer in southern Sweden. International journal of cancer 125(2): 421-5	
Felix, Ashley S, Arem, Hannah, Trabert, Britton et al. (2015) Menopausal hormone therapy and mortality among endometrial cancer patients in the NIH-AARP Diet and Health Study. Cancer causes & control : CCC 26(8): 1055-63	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Gambrell, R D Jr (1984) Hormones in the etiology and prevention of breast and endometrial cancer. Southern medical journal 77(12): 1509-15	Comparison - not placebo or no HRT: no comparator group
Gambrell, R D Jr (1978) The prevention of endometrial cancer in postmenopausal women with progestogens. Maturitas 1(2): 107-12	Comparison - not placebo or no HRT: no comparator group reported
Grady, D, Gebretsadik, T, Kerlikowske, K et al. (1995) Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstetrics and gynecology 85(2): 304-13	Systematic Review – relevant references checked and excluded because data on HRT use not collected at time of prescription or before the outcome was known
Harris, Benjamin S, Bishop, Katherine C, Kuller, Jeffrey A et al. (2020) Hormonal management of menopausal symptoms in women with a history of gynecologic malignancy. Menopause (New York, N.Y.) 27(2): 243-248	Systematic review - relevant references checked and excluded because population includes management of recurring endometrial cancer
Hill, D A, Weiss, N S, Beresford, S A et al. (2000) Continuous combined hormone replacement therapy and risk of endometrial cancer. American journal of obstetrics and gynecology 183(6): 1456-61	Outcomes - reported outcomes do not match the review protocols
Hunt, K; Vessey, M; McPherson, K (1990) Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. British journal of obstetrics and gynaecology 97(12): 1080-6	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Jaakkola, Susanna, Lyytinen, Heli K, Dyba, Tadeusz et al. (2011) Endometrial cancer associated with various forms of postmenopausal hormone therapy: a case control study. International journal of cancer 128(7): 1644-51	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Jain, M.G.; Rohan, T.E.; Howe, G.R. (2000) Hormone replacement therapy and endometrial cancer in Ontario, Canada. Journal of Clinical Epidemiology 53(4): 385-391	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Jick, S.S.; Walker, A.M.; Jick, H. (1993) Estrogens, progesterone, and endometrial cancer. Epidemiology 4(1): 20-24	Study design - not a systematic review, randomised controlled trial, or observational study
Karageorgi, Stalo, Hankinson, Susan E, Kraft, Peter et al. (2010) Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. International journal of cancer 126(1): 208-16	Population - Mean age of women at baseline was 41.8 years. Included nurses aged 30-55 years
Kling, J M, Lahr, B A, Bailey, K R et al. (2015) Endothelial function in women of the Kronos Early Estrogen Prevention Study. Climacteric:	Outcomes - reported outcomes do not match the review protocols

Study	Reason for exclusion
the journal of the International Menopause Society 18(2): 187-97	
Lacey, James V Jr, Brinton, Louise A, Lubin, Jay H et al. (2005) Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 14(7): 1724-31	Cohort already included (Trabert 2013)
Lacey, James V Jr, Leitzmann, Michael F, Chang, Shih-Chen et al. (2007) Endometrial cancer and menopausal hormone therapy in the National Institutes of Health-AARP Diet and Health Study cohort. Cancer 109(7): 1303-11	Cohort already included (Trabert 2013)
Lete, I., Fiol, G., Nieto, L. et al. (2021) The use of menopausal hormone therapy in women survivors of gynecological cancer: Safety report based on systematic reviews and meta-analysis. European Journal of Gynaecological Oncology 42(5): 1058-1067	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Lethaby, A, Suckling, J, Barlow, D et al. (2004) Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. The Cochrane database of systematic reviews: cd000402	Systematic Review – includes studies where the comparison is not placebo or no HRT. Relevant references checked for inclusion
Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen et al. (2017) Long-term hormone therapy for perimenopausal and postmenopausal women. The Cochrane database of systematic reviews 1: cd004143	Systematic Review – reported outcomes do not match the review protocols. Relevant studies checked for inclusion
McCullough, Marjorie L, Patel, Alpa V, Patel, Roshni et al. (2008) Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 17(1): 73-9	Outcomes - reported outcomes do not match the review protocols: ever and never users only (recency unclear)
Mizunuma, H, Honjo, H, Aso, T et al. (2001) Postmenopausal hormone replacement therapy use and risk of endometrial cancer in Japanese women. Climacteric : the journal of the International Menopause Society 4(4): 293-8	Study design - not a systematic review, randomised controlled trial, or observational study
Newcomb, Polly A and Trentham-Dietz, Amy (2003) Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). Cancer causes & control : CCC 14(2): 195-201	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known.
Notelovitz, M, Varner, RE, Rebar, RW et al. (1997) Minimal endometrial proliferation over a two-year period in postmenopausal women taking 03 mg of unopposed esterified estrogens.	Outcomes - reported outcomes do not match the review protocols

Study	Reason for exclusion
Menopause: the journal of the north american menopause society 4(2): 80-88	
Orgeas, Chantal C, Hall, Per, Wedren, Sara et al. (2009) The influence of menopausal hormone therapy on tumour characteristics and survival in endometrial cancer patients. European journal of cancer (Oxford, England : 1990) 45(17): 3064-73	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Ott, Johannes; Egarter, Christian; Aguilera, Alex (2022) Dydrogesterone after 60 years: a glance at the safety profile. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 38(4): 279-287	Outcomes - reported outcomes do not match the review protocols
Paganini-Hill, A; Ross, R K; Henderson, B E (1989) Endometrial cancer and patterns of use of oestrogen replacement therapy: a cohort study. British journal of cancer 59(3): 445-7	Outcomes - reported outcomes do not match the review protocols: ever users and never users only (recency unclear)
Persson, I R, Adami, H O, Eklund, G et al. (1986) The risk of endometrial neoplasia and treatment with estrogens and estrogen-progestogen combinations. First results of a cohort study after one to four completed years of observation. Acta obstetricia et gynecologica Scandinavica 65(3): 211-7	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Persson, I., Yuen, J., Bergkvist, L. et al. (1996) Cancer incidence and mortality in women receiving estrogen and estrogen- progestin replacement therapy - Long-term follow-up of a Swedish cohort. International Journal of Cancer 67(3): 327-332	Comparison - not placebo or no HRT
Phipps, Amanda I, Doherty, Jennifer A, Voigt, Lynda F et al. (2011) Long-term use of continuous-combined estrogen-progestin hormone therapy and risk of endometrial cancer. Cancer causes & control: CCC 22(12): 1639-46	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Pike, M C, Peters, R K, Cozen, W et al. (1997) Estrogen-progestin replacement therapy and endometrial cancer. Journal of the National Cancer Institute 89(15): 1110-6	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Pike, M C and Ross, R K (2000) Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. Steroids 65(1011): 659-64	Study design - not a systematic review, randomised controlled trial, or observational study: Comment
Razavi, Pedram, Pike, Malcolm C, Horn-Ross, Pamela L et al. (2010) Long-term postmenopausal hormone therapy and endometrial cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 19(2): 475-83	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Reed, Susan D, Voigt, Lynda F, Beresford, Shirley A A et al. (2004) Dose of progestin in postmenopausal-combined hormone therapy and risk of endometrial cancer. American journal of obstetrics and gynecology 191(4): 1146-51	Outcomes - reported outcomes do not match the review protocols.

Study	Reason for exclusion
Sayedali, E.; Abdel-Rhman, R.; Yalin, S. (2022) Combined Hormonal Replacement Therapy and The Risk of Endometrial Cancer in Postmenopausal Women: A Meta-analysis. Indian Journal of Gynecologic Oncology 20(4): 41	Systematic Review – includes observational studies where data on HRT use not collected at time of prescription or before the outcome was known. Relevant studies checked for inclusion
Samsioe, G, Boschitsch, E, Concin, H et al. (2006) Endometrial safety, overall safety and tolerability of transdermal continuous combined hormone replacement therapy over 96 weeks: a randomized open-label study. Climacteric: the journal of the International Menopause Society 9(5): 368-79	Comparison - not placebo or no HRT
Simin, Johanna, Khodir, Habiba, Fornes, Romina et al. (2022) Association between menopausal hormone therapy use and mortality risk: a Swedish population-based matched cohort study. Acta oncologica (Stockholm, Sweden) 61(5): 632-640	Outcomes - reported outcomes do not match the review protocols.
Simin, Johanna, Tamimi, Rulla, Lagergren, Jesper et al. (2017) Menopausal hormone therapy and cancer risk: An overestimated risk?. European journal of cancer (Oxford, England: 1990) 84: 60-68	Comparison - not placebo or no HRT
Sjogren, Lea L; Morch, Lina S; Lokkegaard, Ellen (2016) Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas 91: 25-35	Systematic Review – includes observational studies where data on HRT use not collected at time of prescription or before the outcome was known. Relevant studies checked for inclusion
Steinberg, Julia, Yap, Sarsha, Goldsbury, David et al. (2021) Large-scale systematic analysis of exposure to multiple cancer risk factors and the associations between exposure patterns and cancer incidence. Scientific reports 11(1): 2343	Outcomes - reported outcomes do not match the review protocols
Strom, Brian L, Schinnar, Rita, Weber, Anita L et al. (2006) Case-control study of postmenopausal hormone replacement therapy and endometrial cancer. American journal of epidemiology 164(8): 775-86	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Stute, P.; Neulen, J.; Wildt, L. (2016) The impact of micronized progesterone on the endometrium: a systematic review. Climacteric 19(4): 316-328	Systematic Review - included studies where HRT was not oestrogen-only, or combined oestrogen and progestogen. Relevant studies checked for inclusion
Tempfer, Clemens B, Hilal, Ziad, Kern, Peter et al. (2020) Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers 12(8)	Systematic Review – includes observational studies where data on HRT use not collected at time of prescription or before the outcome was known. Relevant studies checked for inclusion
Vickers, Madge R, Martin, Jeannett, Meade, Tom W et al. (2007) The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC women's health 7: 2	Outcomes - reported outcomes do not match the review protocols
Voigt, L F, Weiss, N S, Chu, J et al. (1991) Progestagen supplementation of exogenous oestrogens and risk of endometrial cancer. Lancet (London, England) 338(8762): 274-7	Study design - not a systematic review, randomised controlled trial, or observational study

Study	Reason for exclusion
Wan, Y.-L. and Holland, C. (2011) The efficacy of levonorgestrel intrauterine systems for endometrial protection: A systematic review. Climacteric 14(6): 622-632	Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Weiderpass, E, Adami, H O, Baron, J A et al. (1999) Risk of endometrial cancer following estrogen replacement with and without progestins. Journal of the National Cancer Institute 91(13): 1131-7	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Weiderpass, E, Baron, J A, Adami, H O et al. (1999) Low-potency oestrogen and risk of endometrial cancer: a case-control study. Lancet (London, England) 353(9167): 1824-8	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known
Wiegratz, Inka and Kuhl, Herbert (2005) Endometrial cancer and hormone-replacement therapy. Lancet (London, England) 366(9481): 201-2	Study design - not a systematic review, randomised controlled trial, or observational study: Correspondence
Zucchetto, Antonella, Serraino, Diego, Polesel, Jerry et al. (2009) Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP) 18(4): 316-21	Study design - observational study: data on HRT use not collected at time of prescription or before the outcome was known

Excluded economic studies

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

Appendix K Research recommendations – full details

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

The committee agreed research recommendations 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 are not taking gender-affirming hormone therapy at the time of taking HRT or in the follow-up period
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

Appendix L Study outcomes

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

Table 28: Randomised controlled study data

Trial name	Study ID	Arm 1	Sequential, Continuous, Any	Arm 1, N randomised	Arm 1, N analysed	Arm 1, N events	Arm 2	Arm 2, N randomised	Arm 2, N analysed	Arm 2, N events	Hazard ratios (if reported)	Confidence interval
Incidence of endometrial cancer												
WHI	Roussow 2002 (WHI 2002)	Combined	Continuous	8,506	8,506	22	Placebo	8,102	8,102	25	0.83	0.47 to 1.47
	Roussow 2002 (WHI 2002)	Combined	Continuous	8,506	8,506	20	Placebo	8,102	8,102	16	NA	NA
	Prentice 2009	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Manson 2013	Combined		8,506	8,506	27	Placebo	8,102	8,102	30	0.83	0.49 to 1.40
	Chlebowski 2016	Combined		8,506	8,506	25	Placebo	8,102	8,102	30	0.77	0.45 to 1.31
	Manson 2013	Combined		8,506	8,506	68	Placebo	8,102	8,102	96	0.67	0.49 to 0.91
	Chlebowski 2016	Combined		8,506	8,506	66	Placebo	8,102	8,102	95	0.65	0.48 to 0.89
	Chlebowski 2016	Combined		8,506	5,616	60	Placebo	8,102	5,317	78	NR	NR
	Chlebowski 2016	Combined		8,506	406	3	Placebo	8,102	401	9	NR	NR
	Chlebowski 2016	Combined		8,506	4,518	57	Placebo	8,102	4,253	94	NA	NA
	Prentice 2021	Combined		8,506	NR	97	Placebo	8,102	NR	127	NR	NR
	Heiss 2008	Combined		8,506	8,506	44	Placebo	8,102	8,102	52	NA	NA
	Heiss 2008	Combined		NR	8,052	17	Placebo	NR	7,678	21	NR	NR
HERS	Hulley 1998	Combined		1,380	1,380	2	Placebo	1,383	1,383	4	0.49	0.09 to 2.68

Trial name	Study ID	Arm 1	Sequential, Continuous, Any	Arm 1, N randomised	Arm 1, N analysed	Arm 1, N events	Arm 2	Arm 2, N randomised	Arm 2, N analysed	Arm 2, N events	Hazard ratios (if reported)	Confidence interval
	Hulley 2002	Combined		1,380	Unclear	2	Placebo	1,383	Unclear	5	0.39	0.08 to 2.02
	Hulley 2002	Combined		1,156	Unclear	0	Placebo	1,165	Unclear	3	NA	NA
	Hulley 2002	Combined		1,380	Unclear	2	Placebo	1,383	Unclear	8	0.25	0.05 to 1.18
ESPRIT	Cherry 2002	Oestrogen-only		513	513	0	Placebo	504	504	0	NA	NA
	Cherry 2014	Oestrogen-only		513	513	1	Placebo	504	504	2	0.52	0.05 to 5.80
	Byrjalsen 1999	Combined	Continuous	55	34	1	Placebo	56	43	0	NA	NA
	Byrjalsen 1999	Combined	Sequential	55	27	0	Placebo	56	43	0	NA	NA
	Byrjalsen 1999	Combined	Sequential	56	30	0	Placebo	56	43	0	NA	NA
	Byrjalsen 1999	Combined	Sequential	56	34	0	Placebo	56	43	0	NA	NA
	Byrjalsen 1999 (total HRT groups combined)	Combined		NR	125	1	NA	NR	43	0	NR	NR
	Ferenczy 2002	Combined	Sequential	117	100	1	Placebo	113	63	0	NA	NA
	Ferenczy 2002	Combined	Sequential	114	95	0	Placebo	113	63	0	NA	NA
	Ferenczy 2002	Combined	Sequential	117	88	0	Placebo	113	63	0	NA	NA
	Ferenczy 2002	Combined	Sequential	118	96	2	Placebo	113	63	0	NA	NA
	Ferenczy 2002 (total HRT groups combined)	Combined		NR	379	3	NA	NR	63	0	NR	NR
OPAL	Langer 2006	Combined		284	236	0	Placebo	287	243	1	NA	NA
	Nachtigall 1979	Combined	Continuous	84	84	0	Placebo	84	84	1	NA	NA
	Obel 1993	Combined	Sequential	50	45	0	Placebo	51	45	0	NA	NA
	Obel 1993	Combined	Continuous	50	39	0	Placebo	51	45	0	NA	NA
	Obel 1993 (total HRT groups combined)	Combined		NR	84	0	NA	NR	45	0	NR	NR

Trial name	Study ID	Arm 1	Sequential, Continuous, Any	Arm 1, N randomised	Arm 1, N analysed	Arm 1, N events	Arm 2	Arm 2, N randomised	Arm 2, N analysed	Arm 2, N events	Hazard ratios (if reported)	Confidence interval
	PEPI 1995	Oestrogen-only	Continuous	119	119	0	Placebo	119	119	1	NA	NA
	PEPI 1995	Combined	Cyclical / sequential	118	118	0	Placebo	119	119	1	NA	NA
	PEPI 1995	Combined	Continuous	120	120	0	Placebo	119	119	1	NA	NA
	PEPI 1995	Combined	Cyclical / sequential	120	120	0	Placebo	119	119	1	NA	NA
	PEPI 1995 (total HRT treatment groups combined)	Combined		NR	358	0	NA	NR	119	1	NR	NR
WHI	Manson 2013	Combined		NR	2,837	6	Placebo	NR	2683	5	NR	NR
	Manson 2013	Combined		NR	3,854	14	Placebo	NR	3655	17	NR	NR
	Manson 2013	Combined		NR	1,815	7	Placebo	NR	1764	8	NR	NR
	Manson 2013	Combined		NR	2,837	22	Placebo	NR	2683	31	NR	NR
	Manson 2013	Combined		NR	3,854	32	Placebo	NR	3655	44	NR	NR
	Manson 2013	Combined		NR	1,815	14	Placebo	NR	1764	21	NR	NR
	Chlebowski 2016	Combined		NR	846	7	Placebo	NR	767	11	NR	NR
	Chlebowski 2016	Combined		NR	1420	15	Placebo	NR	1361	20	NR	NR
	Chlebowski 2016	Combined		NR	3019	31	Placebo	NR	2887	43	NR	NR
	Chlebowski 2016	Combined		NR	1260	13	Placebo	NR	1228	21	NR	NR
Mortality from Endometrial Cancer												
WHI	Chlebowski 2016	Oestrogen + progestin	NA	8506	8506	5	Placebo	8102	8102	11	0.42	0.15 to 1.22
ESPRIT	Cherry 2014	Oestrogen	NA	513	513	0	Placebo	504	504	0	NA	NA

CEE: conjugated equine oestrogens; ESPRIT: European/Australasian Stroke Prevention in Reversible Ischaemia Trial; HERS: Heart and Estrogen/progestin Replacement Study; HRT: hormone replacement therapy; NA: not applicable; NR: not reported; OPAL: Occupational support for patients undergoing Arthroplasty of the Lower limb Trial; PEPI: Postmenopausal Estrogen/Progestin Interventions; RCT: randomised controlled trial; WHI: Women's Health Initiative.

Table 29: Observational study data

Trial name	Study ID	N	Subgroups	Arm 1	Sequential, Continuous, Any	Arm 2	Effect estimate (95% CI)
EPIC	Allen 2010	115,474	Years of use: <2	Oestrogen + progestogen	Any	No HRT	HR 1.46 (0.94 to 2.27)
			Years of use: >2	Oestrogen + progestogen	Any	No HRT	HR 1.64 (1.11 to 2.42)
			Years of use: Any duration of use	Oestrogen + progestogen	Sequential	No HRT	HR 1.52 (1.00 to 2.31)
				Oestrogen + progestogen	Continuous	No HRT	HR 0.24 (0.08 to 0.72)
			By BMI: <25	Oestrogen + progestogen	Any	No HRT	HR 1.49 (1.05 to 2.11)
			By BMI: 25-29	Oestrogen + progestogen	Any	No HRT	HR 1.24 (0.74 to 2.08)
			By BMI: ≥30	Oestrogen + progestogen	Any	No HRT	HR 1.29 (0.65 to 2.56)
NOWAC	Bakken 2004	27,621	Years of use: Any duration of use	Oestrogen-only		No HRT	HR 3.20 (1.20 to 8.53)
				Oestrogen + progestogen	Any	No HRT	HR 0.70 (0.40 to 1.22)
			By constituent: oestriol	Oestrogen-only		No HRT	HR 3.10 (1.20 to 8.01)
MWS	Beral 2005	716,738	Years of use: <5	Oestrogen + progestogen	Continuous	No HRT	RR 0.55 (0.37 to 0.82)
			Years of use: ≥5	Oestrogen + progestogen	Continuous	No HRT	RR 0.90 (0.66 to 1.23)
			By constituent: norethisterone	Oestrogen + progestogen	Continuous	No HRT	RR 0.76 (0.57 to 1.01)
			By constituent: MPA	Oestrogen + progestogen	Continuous	No HRT	RR 0.63 (0.43 to 0.92)
			By BMI: <25	Oestrogen + progestogen	Continuous	No HRT	RR 1.07 (0.73 to 1.57)
			By BMI: 25-29	Oestrogen + progestogen	Continuous	No HRT	RR 0.88 (0.60 to 1.29)
			By BMI: ≥30	Oestrogen + progestogen	Continuous	No HRT	RR 0.28 (0.14 to 0.56)
E3N	Fournier 2014	65,630	-	Oestrogen-only		No HRT	HR 3.30 (1.61 to 6.76)
			By constituent: micronized progesterone	Oestrogen + progestogen	Any	No HRT	HR 1.96 (1.41 to 2.72)
			By constituent: dydrogesterone	Oestrogen + progestogen	Any	No HRT	HR 0.67 (0.36 to 1.25)
			By constituent: other progesterone derivative	Oestrogen + progestogen	Any	No HRT	HR 0.65 (0.41 to 1.03)
	Gambrell 1979	NR	Years of use: ≥15	Oestrogen-only		No HRT	RR 1.93 (0.51 to 7.30)

Trial name	Study ID	N	Subgroups	Arm 1	Sequential, Continuous, Any	Arm 2	Effect estimate (95% CI)
				Oestrogen + progestogen	Any	No HRT	RR 0.27 (0.04 to 1.82)
The Diet, Cancer, and Health cohort	Holm 2018	29,152	Years of use: ≥15	Oestrogen-only		No HRT	RR 2.38 (1.50 to 3.78)
				Oestrogen + progestogen	Any	No HRT	RR 1.86 (1.42 to 2.44)
PLCO	Liang 2021	45,203	-	Oestrogen-only		No HRT	HR 1.51 (1.12 to 2.04)
			Years of use: <1	Oestrogen-only		No HRT	HR 0.91 (0.47 to 1.76)
				Oestrogen + progestogen	Any	No HRT	HR 1.20 (0.83 to 1.73)
			Years of use: 1-3	Oestrogen-only		No HRT	HR 0.45 (0.19 to 1.07)
				Oestrogen + progestogen	Any	No HRT	HR 1.04 (0.71 to 1.52)
			Years of use: 3-5	Oestrogen-only		No HRT	HR 1.21 (0.67 to 2.19)
				Oestrogen + progestogen	Any	No HRT	HR 0.69 (0.41 to 1.16)
			Years of use: 5-10	Oestrogen-only		No HRT	HR 1.37 (0.82 to 2.29)
				Oestrogen + progestogen	Any	No HRT	HR 1.00 (0.65 to 1.54)
			Years of use: >10	Oestrogen-only		No HRT	HR 2.92 (2.06 to 4.14)
				Oestrogen + progestogen	Any	No HRT	HR 0.59 (0.30 to 1.16)
			By route of administration: oral	Oestrogen-only		No HRT	HR 2.23 (1.53 to 325)
			By route of administration: transdermal	Oestrogen-only		No HRT	HR 1.59 (1.02 to 2.48)
			By BMI: <25	Oestrogen-only		No HRT	HR 2.75 (1.79 to 4.23)
			By BMI: 25-30	Oestrogen-only		No HRT	HR 1.31 (0.89 to 1.93)
			By BMI: >30	Oestrogen-only		No HRT	HR 0.56 (0.38 to 0.83)
			Years of use: Any duration of use	Oestrogen + progestogen	Any	No HRT	HR 0.93 (0.72 to 1.20)
	Morch 2016	914,595	-	Oestrogen-only		No HRT	RR 2.70 (2.41 to 3.03)
			Years of use: Any duration of use	Oestrogen + progestogen	Continuous	No HRT	RR 1.02 (0.87 to 1.20)
			By constituent: conjugated oestrogen	Oestrogen-only		No HRT	RR 4.27 (1.92 to 9.50)

Trial name	Study ID	N	Subgroups	Arm 1	Sequential, Continuous, Any	Arm 2	Effect estimate (95% CI)
			By constituent: non-conjugated oestrogen	Oestrogen-only		No HRT	RR 2.00 (1.87 to 2.14)
			By constituent: norethisterone	Oestrogen + progestogen	Continuous	No HRT	RR 1.01 (0.86 to 1.19)
			By route of administration: oral	Oestrogen-only		No HRT	RR 2.71 (2.40 to 3.06)
				Oestrogen + progestogen	Continuous	No HRT	RR 1.01 (0.86 to 1.19)
			By route of administration: transdermal	Oestrogen-only		No HRT	RR 2.77 (2.12 to 3.62)
				Oestrogen + progestogen	Continuous	No HRT	RR 0.74 (0.18 to 3.04)
	Schneider 2009	69,412	By constituent: oestradiol + dydrogesterone	Oestrogen + progestogen	Any	No HRT	OR 0.98 (0.24 to 4.00)
			By constituent: oestradiol + norethisterone	Oestrogen + progestogen	Any	No HRT	OR 0.57 (0.26 to 1.25)
			By constituent: CEE + norgestrel	Oestrogen + progestogen	Any	No HRT	OR 0.73 (0.33 to 1.61)
			By constituent: CEE + MPA	Oestrogen + progestogen	Any	No HRT	OR 0.89 (0.40 to 1.98)
BWHS	Sponholtz 2018	47,555	Years of use: 1-4	Oestrogen-only		No HRT	IRR 1.25 (0.70 to 2.23)
				Oestrogen + progestogen	Any	No HRT	IRR 0.79 (0.47 to 1.33)
			Years of use: ≥5	Oestrogen-only		No HRT	IRR 1.90 (0.59 to 6.12)
				Oestrogen + progestogen	Any	No HRT	IRR 0.99 (0.49 to 2.00)
			By BMI: <30	Oestrogen-only		No HRT	IRR 5.05 (1.42 to 17.96)
				Oestrogen + progestogen	Any	No HRT	IRR 1.65 (0.55 to 4.95)
			By BMI: ≥30	Oestrogen-only		No HRT	IRR 5.16 (1.51 to 17.63)
				Oestrogen + progestogen	Any	No HRT	IRR 0.48 (0.09 to 2.56)
NIH-AARP	Trabert 2013	68,419	Years of use: <10	Oestrogen-only		No HRT	RR 0.78 (0.42 to 1.45)
				Oestrogen + progestogen	Any	No HRT	RR 1.30 (0.54 to 3.13)
				Oestrogen + progestogen	Sequential	No HRT	RR 0.90 (0.64 to 1.27)
			Years of use: ≥10	Oestrogen-only		No HRT	RR 5.04 (3.18 to 7.99)

Trial name	Study ID	N	Subgroups	Arm 1	Sequential, Continuous, Any	Arm 2	Effect estimate (95% CI)
				Oestrogen + progestogen	Any	No HRT	RR 1.44 (1.11 to 1.87)
				Oestrogen + progestogen	Sequential	No HRT	RR 1.88 (1.36 to 2.60)
			By BMI: <25	Oestrogen-only		No HRT	RR 4.31 (2.43 to 7.64)
				Oestrogen + progestogen	Any	No HRT	RR 1.78 (1.28 to 2.48)
			By BMI: 25-<30	Oestrogen-only		No HRT	RR 2.35 (1.27 to 4.35)
				Oestrogen + progestogen	Any	No HRT	RR 0.98 (0.71 to 1.35)
			By BMI: ≥30	Oestrogen-only		No HRT	RR 0.40 (0.13 to 1.26)
				Oestrogen + progestogen	Any	No HRT	RR 0.47 (0.33 to 0.67)

BMI: body mass index; BWHS: Black Women's Health Study; CI: confidence interval; DCHC: The Diet, Cancer, and Health cohort; E3N: Étude épidemiologique des femmes de la Mutuelle Générale de l'Education Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; HRT: hormone replacement therapy; IQR: interquartile range; IRR: incidence rate ratio; MWS: Million Women Study; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NOWAC: Norwegian Women and Cancer Study; NR: not reported; OR: odds ratio; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RR: risk ratio.

Appendix M 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 endometrial cancer?

Absolute risks were calculated according to age. For certain subgroups (constituent; BMI; route of administration) it was not possible to calculate the absolute risks due to lack of information on their background risks.

Table 30: Summary of endometrial cancer cases with current use of combined HRT in people who, if they used it, started HRT at 50, with an unknown duration of use

	50+ years old
Number of endometrial cancer cases over a 5-year period per 1000 people who are not HRT users	4
Number of endometrial cancer cases over a 5-year period per 1000 people who are combined HRT (sequential) users	8 (from 6 to 11)
Number of endometrial cancer cases over a 5-year period per 1000 people who are combined HRT (continuous) users	1 (from 0 to 3)

Table 31: Summary of endometrial cancer cases with current use of oestrogen-only HRT in people who, if they used it, started HRT at 50, with an unknown duration of use

	50+ years old
Number of endometrial cancer cases over a 5-year period per 1000 people who are not HRT users	4
Number of endometrial cancer cases over a 5-year period per 1000 people who are oestrogen-only HRT users	11 (from 10 to 12)

Calculations

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

The rate of endometrial 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 endometrial cancer in never users

RRcurrent = The average endometrial cancer relative risk for HRT users versus never users [RR (current vs never users)] in the general population and is taken from the risks calculated in this review, assuming ¼ of HRT users use oestrogen-only and ¾ use combined HRT. An average of the risks for sequential and continuous combined HRT was used for the combined HRT risk. Therefore, this gives an average RR of 1.76.

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 endometrial cancer registration statistics for 2017.

See Supplement 19 for calculations.

Absolute risks using randomised controlled trial data

Table 32: Number of endometrial cancer cases with no use and current use of combined HRT in people who, if they used it, started HRT at 63 and used it for 5-9 years

	63-69 years old
Number of endometrial cancer cases over an approximate 5-9-year period per 1000 people who never used HRT	4
Number of endometrial cancer cases over an approximate 5-9-year period per 1000 people who started HRT at 63 and used for approximately 6 years	3 (from 2 to 5) NS

Table 33: Number of endometrial cancer cases with no use and current use of oestrogen- only HRT in people who, if they used it, started HRT at 63 and used it for 1-4 years

	56-63 years old
Number of endometrial cancer cases over an approximate 3-year period per 1000 people who never used HRT	2
Number of endometrial cancer cases over an approximate 3-year period per 1000 people who started HRT between 56 and 63 and used for 1-4 years	0 (from 0 to 11) NS