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Long-term hormone therapy for perimenopausal and postmenopausal women (Review)

Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J

Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J.
Long-term hormone therapy for perimenopausal and postmenopausal women.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD004143.
DOI: [10.1002/14651858.CD004143.pub5](https://doi.org/10.1002/14651858.CD004143.pub5).

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[Intervention Review]

Long-term hormone therapy for perimenopausal and postmenopausal women

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Editorial group: Cochrane Gynaecology and Fertility Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 1, 2017.

Citation: Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD004143. DOI: [10.1002/14651858.CD004143.pub5](https://doi.org/10.1002/14651858.CD004143.pub5).

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ABSTRACT

Background

Hormone therapy (HT) is widely provided for control of menopausal symptoms and has been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005.

Objectives

To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment.

Search methods

We searched the following databases to September 2016: Cochrane Gynaecology and Fertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO. We searched the registers of ongoing trials and reference lists provided in previous studies and systematic reviews.

Selection criteria

We included randomised double-blinded studies of HT versus placebo, taken for at least 1 year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via the oral, transdermal, subcutaneous or intranasal route.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias and extracted data. We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data, along with 95% confidence intervals (CIs). We assessed the quality of the evidence by using GRADE methods.

Main results

We included 22 studies involving 43,637 women. We derived nearly 70% of the data from two well-conducted studies (HERS 1998; WHI 1998). Most participants were postmenopausal American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women.

In relatively healthy postmenopausal women (i.e. generally fit, without overt disease), combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per

1000 to between 4 and 11 per 1000), stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000), breast cancer (after 5.6 years' use: from 19 per 1000 to between 20 and 30 per 1000), gallbladder disease (after 5.6 years' use: from 27 per 1000 to between 38 and 60 per 1000) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000).

Oestrogen-only HT increased the risk of venous thromboembolism (after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000; after 7 years' use: from 16 per 1000 to 16 to 28 per 1000), stroke (after 7 years' use: from 24 per 1000 to between 25 and 40 per 1000) and gallbladder disease (after 7 years' use: from 27 per 1000 to between 38 and 60 per 1000) but reduced the risk of breast cancer (after 7 years' use: from 25 per 1000 to between 15 and 25 per 1000) and clinical fracture (after 7 years' use: from 141 per 1000 to between 92 and 113 per 1000) and did not increase the risk of coronary events at any follow-up time.

Women over 65 years of age who were relatively healthy and taking continuous combined HT showed an increase in the incidence of dementia (after 4 years' use: from 9 per 1000 to 11 to 30 per 1000). Among women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism (at 1 year's use: from 3 per 1000 to between 3 and 29 per 1000). Women taking HT had a significantly decreased incidence of fracture with long-term use.

Risk of fracture was the only outcome for which strong evidence showed clinical benefit derived from HT (after 5.6 years' use of combined HT: from 111 per 1000 to between 79 and 96 per 1000; after 7.1 years' use of oestrogen-only HT: from 141 per 1000 to between 92 and 113 per 1000). Researchers found no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer.

One trial analysed subgroups of 2839 relatively healthy women 50 to 59 years of age who were taking combined continuous HT and 1637 who were taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: Their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded, as this study was not designed to have the power to detect differences between groups of women within 10 years of menopause.

For most studies, risk of bias was low in most domains. The overall quality of evidence for the main comparisons was moderate. The main limitation in the quality of evidence was that only about 30% of women were 50 to 59 years old at baseline, which is the age at which women are most likely to consider HT for vasomotor symptoms.

Authors' conclusions

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented.

HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for prevention of deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women and in postmenopausal women younger than 50 years of age.

PLAIN LANGUAGE SUMMARY

Long-term hormone therapy for perimenopausal and postmenopausal women

Review question

In perimenopausal and postmenopausal women, what are the clinical effects of using hormone therapy (HT) for a year or longer?

Background

HT is given for control of menopausal symptoms. It has also been used for the management and prevention of chronic diseases such as cardiovascular disease, osteoporosis and dementia.

Study characteristics

This review included 22 double-blinded randomised controlled trials (RCTs) (43,637 women). The evidence is current to September 2016.

Key results

In relatively healthy postmenopausal women, using combined continuous HT for 1 year increased the risk of a heart attack from about 2 per 1000 to between 3 and 7 per 1000, and increased the risk of venous thrombosis (blood clot) from about 2 per 1000 to between 4 and 11 per 1000. With longer use, HT also increased the risk of stroke, breast cancer, gallbladder disease and death from lung cancer.

Oestrogen-only HT increased the risk of venous thrombosis after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000. With longer use, it also increased the risk of stroke and gallbladder disease, but it reduced the risk of breast cancer (after 7 years' use) from 25 per 1000 to between 15 and 25 per 1000.

Among women over 65 years of age taking continuous combined HT, the incidence of dementia was increased.

Risk of fracture was the only outcome for which results showed strong evidence of clinical benefit from HT (both types).

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer for women with a uterus who take oestrogen-only HT is well documented.

HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.

Quality of the evidence

For most studies, risk of bias was low in most domains and the overall quality of the evidence was moderate. The main limitation was that only about 30% of women were 50 to 59 years old at baseline - the age at which women are likely to consider HT for vasomotor symptoms.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Combined continuous hormone therapy (HT) compared with placebo for postmenopausal women

Combined continuous hormone therapy (HT) compared with placebo for perimenopausal and postmenopausal women

Population: relatively healthy postmenopausal women

Setting: community

Intervention: combined continuous HT (moderate-dose oestrogen) - CEE 0.625 mg + MPA 2.5 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk*	Corresponding risk				
	Placebo	Combined continuous hormone therapy (HT)				
Coronary events (MI or cardiac death) Follow-up: mean/median 1 year	2 per 1000	4 per 1000 (3 to 7)	RR 1.89 (1.15 to 3.10)	20,993 (2 studies)	⊕⊕⊕⊖	Moderate^a
Stroke Follow-up: mean 3 years	6 per 1000	8 per 1000 (6 to 12)	RR 146 (1.02 to 2.09)	17,585 (2 studies)	⊕⊕⊕⊖	Moderate^a
Venous thromboembolism (DVT or PE) Follow-up: mean/median 1 year	2 per 1000	7 per 1000 (4 to 11)	RR 4.28 (2.49 to 7.34)	20,993 (2 studies)	⊕⊕⊕⊖	Moderate^a
Breast cancer Follow-up: median 5.6 years	19 per 1000	24 per 1000 (20 to 30)	RR 1.27 (1.03 to 1.56)	16,608 (1 study)	⊕⊕⊕⊖	Moderate^a
Death from lung cancer Follow-up: median 8 years ^b	5 per 1,000	9 per 1000 (6 to 13)	RR 1.74 (1.18 to 2.55)	16,608 (1 study)	⊕⊕⊕⊖	Moderate^a
Gallbladder disease Follow-up: mean 5.6 years	16 per 1000	27 per 1000 (21 to 34)	RR 1.64 (1.30 to 2.06)	14,203 (1 study)	⊕⊕⊕⊖	Moderate^a
All clinical fractures Follow-up: mean 5.6 years	111 per 1000	87 per 1000 (79 to 96)	RR 0.78 (0.71 to 0.86)	16,608 (1 study)	⊕⊕⊕⊖	Moderate^a

*The basis for the **assumed risk** is the mean risk in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
 CI: confidence interval; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded one level for questionable applicability: Only about 33% of the study sample was 50–59 years of age at baseline (i.e. the age women are most likely to consider HT for vasomotor symptoms); mean participant age was 63 years.

^b5.6 years' intervention plus postintervention follow-up: post hoc analysis.

Summary of findings 2. Oestrogen-only hormone therapy (HT) compared with placebo for postmenopausal women

Oestrogen-only hormone therapy (HT) compared with placebo for perimenopausal and postmenopausal women

Population: relatively healthy postmenopausal women

Setting: community

Intervention: oestrogen-only HT (moderate dose)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oestrogen-only hormone therapy (HT)				
Coronary events (MI or cardiac death) Follow-up: mean 7.1 years ^a	41 per 1000	38 per 1000 (32 to 46)	RR 0.94 (0.78 to 1.13)	10,739 (1 study)	⊕⊕⊕⊖ Moderate ^b	
Stroke Follow-up: mean 7.1 years ^a	24 per 1000	32 per 1000 (25 to 40)	RR 1.33 (1.06 to 1.67)	10,739 (1 study)	⊕⊕⊕⊖ Moderate ^b	
Venous thromboembolism (DVT or PE) Follow up 1-2 years	2 per 1000	5 per 1000 (2 to 10)	RR 2.22 (1.12 to 4.39)	10,739 (1 study)	⊕⊕⊕⊖ Moderate ^b	
Venous thromboembolism (DVT or PE):	16 per 1000	21 per 1000 (16 to 28)	RR 1.32 (1.00 to 1.74)	10,739 (1 study)	⊕⊕⊕⊖ Moderate ^b	

CEE 0.625 mg (moderate dose) Follow-up: mean 7.1 years ^a					
Breast cancer Follow-up: mean 7.1 years ^a	25 per 1000	20 per 1000 (15 to 25)	RR 0.79 (0.61 to 1.01)	10,739 (1 study)	⊕⊕⊕ Moderate ^b
Gallbladder disease Follow-up: mean 7.1 years ^a	27 per 1000	47 per 1000 (38 to 60)	RR 1.78 (1.42 to 2.24)	8376 (1 study)	⊕⊕⊕ Moderate ^b
All clinical fractures Follow-up: mean 7.1 years ^a	141 per 1000	103 per 1000 (92 to 113)	RR 0.73 (0.65 to 0.80)	10,739 (1 study)	⊕⊕⊕ Moderate ^b

*The basis for the **assumed risk** is the mean risk in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aMedian use of CEE 5.9 years ([LaCroix 2011](#)).

^bDowngraded one level for questionable applicability: Only 31% of study sample was 50-59 years of age at baseline (i.e. the age women are most likely to consider HT for vasomotor symptoms); mean participant age was 63 years.

BACKGROUND

Description of the condition

The median age at onset of menopause varies across geographical regions. In Europe, it ranges from about 50 to 53 years, in North America from 50 to 51 years, in Latin America from 44 to 53 years and in Asia from 42 to 49 years (Palacios 2010). Most women experience menopause (the last menstrual period) after a phase of changing ovarian function (the perimenopause) that may last several years and is characterised by irregular menstrual cycles (Greendale 1999). Women are said to be postmenopausal when menstruation has ceased for 12 months. Many (although not all) perimenopausal and postmenopausal women report a variety of symptoms, including hot flushes and vaginal dryness, which probably relate to the natural decline in oestrogen levels. Symptoms tend to fluctuate and their severity varies greatly between individuals, with some reporting intense discomfort and a substantial reduction in quality of life. Most research has focused on white women, but the experience of menopause differs between women of different races and ethnicities, as well as by menopausal stage (Avis 2001; Palacios 2010). The duration of regular hot flushes is highly variable. Most women report that hot flushes last from 6 months to 2 years (Kronenberg 1994), but longitudinal research suggests that the time from onset to resolution of symptoms is often considerably longer (Guthrie 2005).

Description of the intervention

Hormone therapy (HT) consists of oestrogen alone (oestrogen-only HT) or oestrogen combined with a progestogen (combined HT). It is available in a variety of formulations and doses that can be taken orally, vaginally or intranasally, or as an implant, skin patch, cream or gel. Clinical effects vary according to the type of HT and its duration of use.

The addition of a progestogen reduces the risk of endometrial hyperplasia associated with the use of oestrogen alone in women with a uterus (Furness 2012), but the issue is problematic because progestogens have adverse effects on blood lipids and may have the potential to cause symptoms such as headache, bloating and breast tenderness (McKinney 1998). Progestogens used for HT include synthetic derivatives of progesterone, synthetic derivatives of testosterone and natural progesterones derived from plants. These differ in their metabolic action and potential for adverse effects, and it is currently unclear which type of progestogen has the best risk-benefit profile for use in HT. In combined HT, progestogen can be taken continuously (every day), sequentially (for part of each month) or less frequently.

Hormone therapy (HT) has been utilised for over 50 years for the treatment of women with hot flushes and other menopausal symptoms, and its efficacy is well established, as evidenced by a Cochrane systematic review of 24 randomised controlled studies of HT for hot flushes that was published between 1971 and 2000 (MacLennan 2004).

During the past 25 years, HT has also been used for the management or prevention of chronic disease. Oestrogens and progestogens affect most body systems and have been proposed as causing or preventing a wide range of conditions. Recommendations for use have varied over time, but through the 1990s, commonly held expert opinion was that most

postmenopausal women could benefit from HT (Hemminki 2000a). This view was based on strong and consistent observational evidence that HT reduced the risk of coronary heart disease (CHD) by at least 30%. A meta-analysis of 25 cohort, case-control and angiographic studies published up to 1997 revealed a risk ratio of 0.70 (95% confidence interval (CI) 0.65 to 0.75) for CHD among oestrogen users compared with never-users.

Other benefits reported in observational studies of HT include strong evidence of a reduction in osteoporotic fractures, a possible preventive or delaying effect on cognitive decline or dementia and even a reduction in overall mortality for current users (Barrett-Connor 1998).

How the intervention might work

Oestrogen has a favourable effect on some biomarkers, including indicators of cardiovascular disease and disorders of bone metabolism. It has been shown to improve endothelial vasodilator function, promote angiogenesis and modulate autonomic function. Thus cardioprotective benefits of oestrogen have some biological plausibility (Miller 2008). However, biomarkers interact via multiple complex pathways, and the overall effect of oestrogen on clinical outcomes cannot be predicted with any certainty. Therefore, trials with clinical endpoints such as myocardial infarction (MI) are necessary (Banks 2009a).

Why it is important to do this review

Observational studies have revealed a range of adverse effects of HT, including doubling or tripling of the risk of thromboembolic events, a large increase in endometrial cancer risk among women taking oestrogen without progestogen, an increased incidence of gallbladder disease and a possible link between HT and breast cancer. The suggestion that HT might increase the risk of breast cancer was supported by evidence of an increase in breast density in a high proportion of women taking oestrogen, but findings have been inconsistent and controversial (Barrett-Connor 1998). The results of a very large observational study conducted in the UK (Beral 2003) raised concerns that current users of both combined and oestrogen-only HT were at increased risk of both incident and fatal breast cancer after relatively short periods of use. The increase in risk was greatest among users of combined HT, with no large variations reported between the effects of specific oestrogens or specific progestogens. Risks were greater if HT use started at around the time of menopause than if it started later. Breast cancer rates were highest among current users of combined HT who began use within 5 years of menopause (Beral 2011).

Coronary heart disease (CHD) is the most common cause of death and morbidity in older women, and it was held that a significant reduction in CHD risk from HT would outweigh any potential adverse effects. However, these uncontrolled studies showed strong potential for selection or compliance bias, or both, with oestrogen-takers more likely to be healthy, well-educated, compliant women with a lower baseline risk of cardiovascular disease. The need for randomised controlled trials has been recognised (Barrett-Connor 2001; Hemminki 2000a). It has been suggested that wide prescribing of HT in the 1990s, despite the lack of randomised evidence of its efficacy and safety, might reflect a conflict between commercial and professional interest groups and good public policy (Hemminki 2000). Randomised controlled trials (RCTs) have failed to demonstrate the marked CHD benefits of HT

seen in observational studies and have raised questions about its overall risk-benefit profile.

Other Cochrane reviews have found strong evidence that HT is effective in treating women with menopausal symptoms. One review reported a 75% reduction in the frequency of hot flushes among perimenopausal and postmenopausal women taking HT, relative to placebo, and a statistically significant reduction in symptom severity for the HT group (odds ratio (OR) 0.13, 95% CI 0.07 to 0.23) ([MacLennan 2004](#)). Another review found that local oestrogens were more effective in relieving the symptoms of vaginal atrophy among postmenopausal women when compared with placebo or non-hormonal gel ([Suckling 2006](#)). However, women contemplating the use of HT for menopausal symptoms must be aware of negative findings in other areas, as discussed below.

Previous and forthcoming Cochrane systematic reviews of HT in perimenopausal and postmenopausal women will explore the following topics.

1. Cardiovascular disease ([Boardman 2015](#)).
2. Dementia and cognitive function ([Hogervorst 2009; Lethaby 2008](#)).
3. Endometrial hyperplasia ([Furness 2012](#)).
4. Hot flushes ([MacLennan 2004](#)).
5. Pelvic organ prolapse ([Ismail 2010](#)).
6. Sexual function ([Nastri 2012](#)).
7. Urinary incontinence ([Cody 2009](#)).
8. Vaginal atrophy ([Suckling 2006](#)).
9. Weight and body fat distribution ([Kongnyuy 1999](#)).

In view of the large number of reviews on individual aspects of HT, review authors recognised the need for a systematic review that would provide an overview of all relevant long-term clinical outcomes, thereby providing assistance to women and their clinicians who must make informed judgements about the use of HT. An a priori decision was made to exclude studies of duration shorter than 1 year and not to include as outcomes menopausal symptom control, early-onset side effects of HT and surrogate measures such as endometrial hyperplasia and bone mineral density. This review is not intended to replace other Cochrane reviews on HT, including those listed above. These reviews remain an important source of evidence on individual aspects of HT and will continue to be updated regularly.

This is an updated version of the original Cochrane review first published in 2005.

OBJECTIVES

To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double-blinded studies, which we defined as provided blinding of participants and all researchers and outcome assessors.

For cross-over studies, we intended to use only results from the end of the first phase (before the treatment cross-over) because of the potential carry-over effect of HT therapy from the first treatment phase. However, we identified no cross-over studies for inclusion.

Types of participants

Eligible participants were perimenopausal or postmenopausal women recruited from any healthcare setting or a population-based sample.

Perimenopausal women were defined as women who had not yet had their final menstrual period but were in the transitional period between more-or-less regular cycles of ovulation and menstruation and complete cessation of these cycles.

Postmenopausal women were defined as women with surgical menopause (removal of both ovaries) and women with spontaneous menopause and amenorrhoea for longer than 12 months.

Studies included women both with and without a prior history of disease (e.g. cardiovascular disease, fracture, osteoporosis).

Types of interventions

All oestrogens, with and without progestogens, administered by oral, transdermal, subcutaneous or intranasal routes, and given as perimenopausal or postmenopausal therapy for any reason for 12 months or longer, compared with placebo.

Exclusion criteria

We excluded studies with co-interventions that might potentially affect the outcomes being measured and studies of topical vaginal HT creams, topical tablets and rings. These interventions are covered in another Cochrane review ([Suckling 2006](#)).

Our rationale for excluding trials of less than 1 year's duration is that we considered such trials unlikely to be long enough for investigators to report intervention-related clinical events.

Types of outcome measures

We considered only studies reporting at least one of the following outcomes for inclusion in this review.

1. Death from any cause (total mortality).
2. Cause-specific mortality.
3. Coronary events (myocardial infarction or coronary death).
4. Stroke (ischaemic or haemorrhagic) or transient ischaemic attack (TIA).
5. Venous thromboembolism (pulmonary embolism or deep vein thrombosis).
6. Breast cancer.
7. Colorectal cancer.

8. Lung cancer.
9. Endometrial cancer.
10. Ovarian cancer.
11. Gallbladder disease.
12. Fractures (hip fracture, clinically diagnosed vertebral fracture, total clinically diagnosed fracture).
13. Cognitive function (using global measures) or dementia (including Alzheimer's disease) as measured in the included studies.

We planned to restrict our focus to long-term clinical outcomes and to not include menopausal symptom control and early-onset side effects of HT as outcomes. HT for control of hot flushes is the topic of another systematic review ([MacLennan 2004](#)).

We restricted inclusion to studies reporting one of our outcomes of interest because HT may be studied in the same population for different purposes, and we wished to ensure that we included only relevant studies.

Search methods for identification of studies

We searched for all published and unpublished double-blinded RCTs of HT versus placebo, without language restriction and in consultation with the Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We performed electronic searches of the Cochrane Gynaecology and Fertility Group (CGF) Trials Register (5 September 2016; Procite platform; [Appendix 1](#)), the Cochrane Central Register of Controlled Trials (CENTRAL) Online (5 September 2016; CRSO platform; [Appendix 2](#)), MEDLINE (1966 to 5 September 2016; Ovid platform; [Appendix 3](#)), Embase (1980 to 5 September 2016; Ovid platform; [Appendix 4](#)), PsycINFO (2010 to 5 September 2016; Ovid platform; [Appendix 5](#)) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to September 2016; EBSCO platform; [Appendix 6](#)). We did not restrict the search by language. The GGF Information Specialist designed the search strategy.

We also searched the following trial registers for ongoing and registered trials ([Appendix 7](#)).

1. <http://www.clinicaltrials.gov> (a service of the US National Institutes of Health).
2. <http://www.who.int/trialsearch/Default.aspx> (search portal of the World Health Organization International Trials Registry Platform).

Searching other resources

We checked the reference lists of relevant publications returned by the above searches.

We contacted the following pharmaceutical companies in December 2003, via their websites or by letter, to request data from any published or unpublished randomised controlled trials of HT included in their files: Schering AG, Novartis,

NovoNordisk, Paines and Byrnes/NZMS, 3M Pharmaceuticals, Organon, Wyeth. We received reprints of published studies from one company (NovoNordisk), another company reported that it had no unpublished studies with completed study reports available (Wyeth), and two companies (3M Pharmaceuticals, Organon) acknowledged our request.

We documented the search flow in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart ([Moher 2009](#)).

Data collection and analysis

Selection of studies

One review author screened the titles or abstracts, or both, of all publications obtained by the search strategy to identify potentially eligible studies. If the abstract suggested that the study might be eligible for inclusion, we obtained the full article. Two review authors checked potentially eligible studies against the inclusion criteria of the review. They performed this assessment while unblinded and resolved any uncertainty by discussion. If necessary, we sought additional information from the corresponding author of the study.

Data extraction and management

When studies had multiple publications, the review authors collated multiple reports on the same study, so that each study rather than each report is the unit of interest in the review, and assigned such studies a single study ID with multiple references. Owing to the very large number of publications for some studies (e.g. [WHI 1998](#)), we have on occasion referred in the text to specific papers that are listed under additional references or as sub-publications under the single study ID, to make clear where specific outcomes and time frames are reported.

When no events occurred in either comparison group for a particular outcome, we did not enter data in the [Data and analyses](#) tables for that outcome, in keeping with Cochrane recommendations ([Higgins 2011](#)).

Extracted data included study characteristics and outcome data (see data extraction table for details; [Appendix 8](#)). We corresponded with study investigators to request additional data on methods and/or results, as required.

Assessment of risk of bias in included studies

Two review authors independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool ([Higgins 2011](#)) to examine selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. We resolved disagreements by discussion, or we sought assistance from a third review author. We described all judgements fully and presented our conclusions in the 'Risk of bias table' ([Figure 1](#)), which we incorporated into our interpretation of review findings by performing sensitivity analyses (see below).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Other bias
Barakat 2006	+	+	-	+	+	+	+
ELITE 2014	+	+	?	+	+	+	+
EPAT 2001	+	+	+	+	+	+	+
EPHT 2006	+	+	?	+	+	+	?
ERA 2000	+	+	+	+	+	+	?
ESPRIT 2002	+	+	+	+	+	+	+
EVTET 2000	+	?	+	+	+	+	+
Ferenczy 2002	?	?	-	+	+	+	+
Greenspan 2005	?	+	+	+	+	+	?
HERS 1998	+	+	+	+	+	+	+
KEEPs 2012	+	+	-	+	+	+	+
Mulnard 2000	+	?	+	+	?	+	?
Nachtigall 1979	?	?	+	+	+	+	?
Notelovitz 2002	?	?	+	+	+	+	+
Obel 1993	?	?	?	+	?	+	?
PEPI 1995	+	+	+	+	+	+	?
Tierney 2009	+	+	?	+	?	+	?
WAVE 2002	+	+	+	+	+	+	?
WEST 2001	+	+	+	+	+	+	+
WHI 1998	+	+	+	+	+	+	?

Figure 1. (Continued)

	WHI 1998	+	+	+	+	+	?
	WISDOM 2007	+	+	+	+	+	+
	Yaffe 2006	+	+	+	+	+	+

Measures of treatment effect

We performed statistical analysis according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We analysed treatment effects by comparing outcomes for each group measured at the end of therapy, during ongoing follow-up or at both time points.

For dichotomous data, we generated 2×2 tables for each study and expressed data as risk ratios (RRs) with 95% confidence intervals (CIs). If studies reported the number of events occurring in each comparison group at a mean follow-up time (i.e. not all women had been followed up for that duration of time, and others had been followed up longer), we made the simplifying assumption that risk was constant across the follow-up period and reported data as dichotomous data at a fixed time point. If risk varied significantly across the follow-up period, we noted this variation in the [Results](#) section.

We expressed continuous data as mean differences (MDs) with 95% CIs.

For outcomes for which studies reported no events in the HT nor the placebo group, we did not enter results into data tables.

Unit of analysis issues

The unit of analysis was per woman.

Dealing with missing data

We analysed data on an intention-to-treat basis as far as possible and attempted to obtain missing data from the original trialists. Where these could not be obtained, we analysed only available data.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary, and if this was not the case, we planned to refrain from pooling the data. We assessed statistical heterogeneity by measuring the I^2 statistic. We regarded I^2 greater than 50% as indicating substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the review authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. If we included 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small study effects (tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We planned to pool the results of individual studies (meta-analyse) only when they were clinically similar with respect to study population, intervention and outcome of interest. If an individual study pooled the results of study arms that used different types of HT, we did not include the pooled results in this review.

We combined data for meta-analysis by using RevMan software and the Peto-modified Mantel-Haenszel method. We could reach no consensus about whether a fixed-effect or a random-effects model should be used for meta-analysis, so we performed both types of analysis. This could be viewed as a sensitivity analysis performed to assess the impact of the choice of model on results of the analysis; unless results proved robust to both models, we would have to treat them with caution. Published graphs display results obtained with the fixed-effect model.

We planned to combine continuous data for meta-analysis, had any such data been available for pooling. Meta-analytical methods for continuous data assume that the underlying distribution of measurements is normal. The ratio of the mean to its standard deviation serves as a crude method of assessing skew if this ratio was less than 1.65 for any study group; unless original data were available for log transformation, we did not include the results in analysis tables but reported them in 'Other data' tables. We reported data in the 'Other data' section if they were clearly skewed and if investigators reported results in the publication as median values and ranges with non-parametric tests of significance.

We conducted separate analyses according to the type of HT used (oestrogen only or combined HT). For some outcomes (death, cardiovascular disease, cognition scores), we anticipated that the effect of the intervention might differ according to the clinical status of the participant, and so we conducted separate analyses for studies of women without major health problems and for studies of women with specific health conditions. For other outcomes (cancer, cholelithiasis, fractures), we combined all available study results.

We calculated pooled RRs for all outcomes and translated our main findings into rates per thousand on the basis of rates and confidence intervals per thousand as reported in the 'Summary of findings' tables.

Subgroup analysis and investigation of heterogeneity

If we detected substantial heterogeneity ($> 50\%$), we planned to explore possible explanations by performing subgroup analyses (e.g. different populations) and/or sensitivity analyses (e.g. by risk of bias). We planned to take any statistical heterogeneity into account when interpreting the results, especially if we noted variation in the direction of effect.

Sensitivity analysis

As noted above, we checked whether use of a random-effects model for each analysis materially influenced our findings.

We planned to conduct sensitivity analyses to examine effects of methodological differences between studies provided we identified sufficient studies (> 5). These analyses might help to explain any substantial statistical heterogeneity that may be detected. We planned to explore the following specific differences.

1. Restricting analysis to studies with adequate methods: defined for this purpose as adequate allocation concealment, analysis by intention to treat and losses to follow-up < 10%.
2. Differences among studies with respect to participants, interventions or clinical criteria for defining outcomes, although as noted above, we planned to refrain from combining studies that were obviously dissimilar in these respects.

We planned to conduct additional subgroup or sensitivity analyses if other possible sources of heterogeneity became evident during preparation of the review; however, we would have to interpret the results of any such post hoc analyses with great caution.

Overall quality of the body of evidence: 'Summary of findings' tables

We prepared 'Summary of findings' tables using GRADEpro ([GRADEpro GDT 2014](#)) and Cochrane methods ([Higgins 2011](#)). This table shows the overall quality of the body of evidence for the main comparisons (combined HT and oestrogen-only HT vs placebo) and for the most clinically relevant outcomes (coronary events, stroke, venous thromboembolism, breast cancer, lung cancer, gallbladder disease, clinical fractures) in accordance with GRADE ([Atkins 2004](#)) criteria (study risk of bias, consistency of effect, imprecision,

indirectness and publication bias). We justified judgements about evidence quality (high, moderate, low or very low) and documented and incorporated these judgments into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

Results of search to 2012

We retrieved 57 studies through searches conducted up to 2012 and considered them for inclusion. We included 23 studies and excluded 34 studies.

Search update 2017

We screened 3046 records, discarded 3041 as clearly irrelevant and retained 45 articles, which we checked in full text. From these 44 articles, we identified two new studies: [KEEPs 2012](#) (15 articles) and [ELITE 2014](#) (5 articles). We also identified 20 articles that were additional publications related to studies already included (19 articles for [WHI 1998](#) and one article for [EPHT 2006](#)) and five studies that we excluded ([AHT 2015](#); [Paolletti 2015](#); [Rasgon 2014](#); [Schierbeck 2012](#); [SMART 2016](#)).

For this update of the review, we also excluded three studies that were included in previous versions of the review but that no longer meet our eligibility criteria because we have decided to report fewer outcomes ([Haines 2003](#); [Nielsen 2006](#); [Pefanco 2007](#)). See [Differences between protocol and review](#).

Thus we have included 22 studies and have excluded 42 studies from this review (see [Figure 2](#) for study flow).

Figure 2. Study flow diagram.

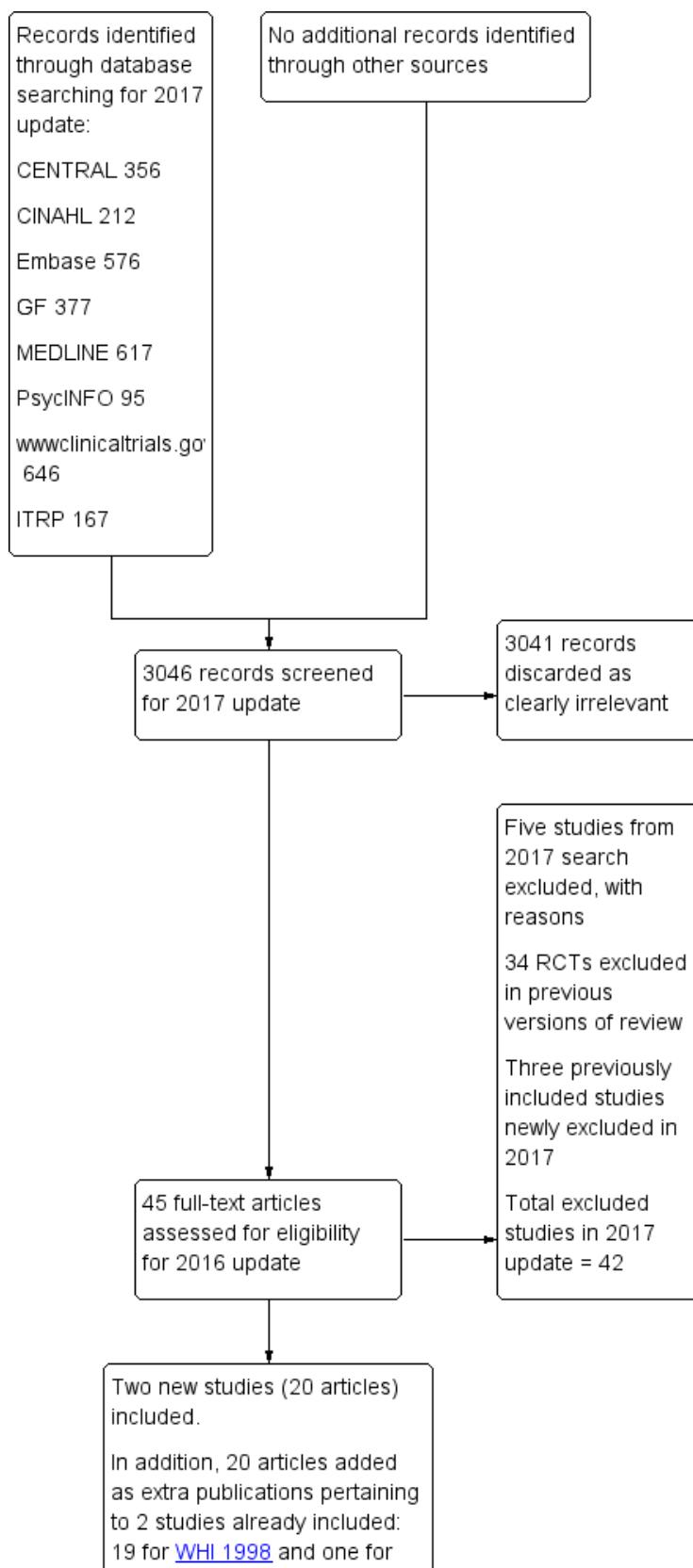
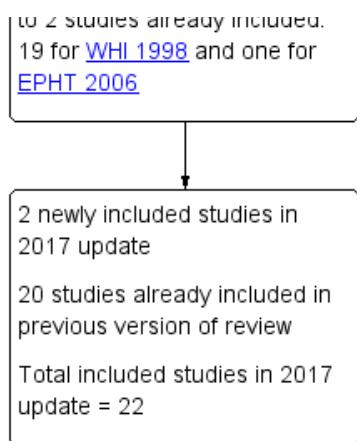


Figure 2. (Continued)


Included studies

The 22 eligible studies are based on one very large study ([WHI 1998](#)). [WHI 1998](#) incorporated randomised comparisons of two different HT regimens versus placebo and published these results separately. One study ([WHI 2002](#)) compared combined oestrogen and progesterone versus placebo and is referred to in this review as [WHI 1998](#) (combined HT arm); the other compared oestrogen-only HT versus placebo and is referred to in this review as [WHI 1998](#) (oestrogen-only HT arm). [WHI 1998](#) also included a subgroup study known as the Women's Health Initiative Memory Study (WHIMS), which measured cognitive outcomes in older women (aged 65 to 79 years at study entry) from both arms of [WHI 1998](#) and is referred to in this review as [WHI 1998](#) (WHIMS) ([Shumaker 1998](#)). An additional ancillary study - [WHI 1998](#) (WHISCA) - enrolled women from [WHI 1998](#) (WHIMS) who were free of dementia to investigate the effects of HT on domain-specific cognitive function in older women ([Resnick 2004](#)).

The 22 identified studies included 43,637 randomised women: 22,693 randomised to some form of HT and 20,928 to placebo (treatment allocation was unclear for 16 women in one study ([Ferenczy 2002](#))). [WISDOM 2007](#) included 1307 additional women who were randomised to a comparison of two active hormone therapies but are not included in this review. Investigators analysed results for more than 99% of these women by intention to treat. Although some studies used biological measures as their primary outcome (e.g. lumen of carotid artery), we included them because they also reported clinical endpoints relevant to this review as prespecified secondary outcomes.

The studies varied dramatically in size. The largest was [WHI 1998](#), which randomised 27,347 participants, and the other studies varied in sample size from 40 ([Tierney 2009](#)) to 5692 ([WISDOM 2007](#)) participants. Investigators included 8000 women in each group in [WHI 1998](#) (combined HT arm) and more than 5000 in each group in [WHI 1998](#) (oestrogen-only HT arm), along with more than 1400 in each group on the oestrogen-only HT arm of [WHI 1998](#) (WHIMS) and more than 2200 in each group on the combined arm of [WHI 1998](#) (WHIMS). [HERS 1998](#) included about 1380 women in each comparison group, [ESPRIT 2002](#) included more than 500 in each group, [EPHT 2006](#) included around 400 women in each group and [KEEPS 2012](#) included 220 to 275 per group. Otherwise, none of the studies included more than 210 women in each group. Five of the smaller studies were single-centred ([ELITE 2014](#); [EPAT 2001](#);

[Nachtigall 1979](#); [Obel 1993](#); [Tierney 2009](#)), and it is unclear whether one study ([EVTET 2000](#)) enlisted more than one trial centre. The other 10 studies involved between 7 and 40 trial centres.

Fourteen studies were conducted in the USA, and one in each of the following countries: UK, Estonia, Norway, Canada and Denmark; three studies were international in scope (one in the USA and Canada, one in Canada and the Netherlands and one in the UK, Australia and New Zealand). Two studies ([EPHT 2006](#); [WISDOM 2007](#)) were originally planned as part of a larger international project, but planning was beset with delays, and in the meantime, [WHI 1998](#) began in the USA when other countries were no longer prepared to commit funds to a second study with similar objectives. Both of these studies were prematurely closed as a result of publication of early [WHI 1998](#) findings.

We attempted to contact investigators for the following studies to request more information about their methods or outcomes: [Barakat 2006](#); [ELITE 2014](#); [EPAT 2001](#); [EVTET 2000](#); [Ferenczy 2002](#); [HERS 1998](#); [KEEPS 2012](#), [Mulnard 2000](#); [Notelovitz 2002](#); [Obel 1993](#); [PEPI 1995](#); [WAVE 2002](#); [WEST 2001](#); [WHI 1998](#), [WISDOM 2007](#). Investigators from the following studies kindly supplied clarification or additional unpublished data, or both: [Barakat 2006](#); [ELITE 2014](#); [ERA 2000](#); [EPHT 2006](#); [HERS 1998](#); [Obel 1993](#); [PEPI 1995](#); [WAVE 2002](#); [WISDOM 2007](#).

Participants

The women included in these studies were predominantly postmenopausal, spontaneously or surgically. The age of participants ranged from 26 to 91 years, with mean or median age of each study ranging from 48 to 76 years (no age was stated in [Obel 1993](#)). In more than half of the studies, mean participant age was over 60 years. Inclusion criteria varied according to the primary objectives of individual studies. Some were designed to investigate the use of HT for treatment of women with menopausal symptoms or for disease prevention and thus enrolled women in reasonably good health. Others were designed to assess whether HT was beneficial for women with a history of cancer or established disease, including heart disease, thromboembolic disease, stroke, Alzheimer's disease or long-term medical conditions requiring hospitalisation; these studies restricted entry to women who had received a diagnosis of the condition of interest.

Studies of women without established medical conditions

Thirteen studies enrolled relatively healthy women ([ELITE 2014](#); [EPAT 2001](#); [EPHT 2006](#); [Ferenczy 2002](#); [Greenspan 2005](#); [KEEPS 2012](#), [Notelovitz 2002](#); [Obel 1993](#); [PEPI 1995](#); [Tierney 2009](#); [WHI 1998](#); [WISDOM 2007](#); [Yaffe 2006](#)). Women in some of these studies had risk factors (such as raised cholesterol), and a small minority within individual studies had a history of cardiovascular disease, but most participants were fit women without overt disease. Most of these studies were interested in the use of HT for disease prevention.

Three studies were large and investigated the use of HT to prevent cardiovascular disease while also reporting a wide range of other endpoints; researchers provided highly detailed lists of inclusion and exclusion criteria ([PEPI 1995](#); [WHI 1998](#), [WISDOM 2007](#)). In [WHI 1998](#), enrolment was targeted to establish set fractions for baseline age categories and to achieve representation of racial and ethnic groups in the proportions recorded by the US census for individuals 50 to 79 years of age.

The [WHI 1998](#) (combined HT arm) investigators noted that prevalence of prior cardiovascular disease in participants was low: 4.4% had a history of myocardial infarction, coronary revascularisation, stroke or transient ischaemic attack. They also commented that levels of cardiovascular risk factors were consistent with a generally healthy population of postmenopausal women: 2.9% reported a history of angina, 36% were hypertensive (or were being treated for hypertension), 13% were being treated for high cholesterol, 4.4% were being treated for diabetes and 10.5% were current smokers ([Manson 2003](#)). Similarly, in [WHI 1998](#) (oestrogen-only HT arm), participants in general were considered healthy, although 4.1% had a history of myocardial infarction or coronary revascularisation, 5.8% had a history of angina, 1.4% had a history of stroke, 1.6% had a history of venous thrombosis, 48% were hypertensive (or were being treated for hypertension), 15% were receiving treatment for high cholesterol, 7.7% were being treated for diabetes and 10.5% were current smokers ([Stefanick 2003](#)).

[PEPI 1995](#) compared the characteristics of their cohort with values returned in large US surveys and concluded that although the [PEPI 1995](#) cohort was generally in better health than the wider US population, these individuals were not so markedly different as to limit the generalisability of study results. Both [KEEPS 2012](#) and [ELITE 2014](#) were designed to test whether menopausal HT initiated soon after menopause could delay progression of atherosclerosis. Two other 'prevention' studies aimed to test the possible beneficial effects of HT on arterial wall density ([EPAT 2001](#)) and bone density ([Notelovitz 2002](#)). Four much smaller studies also enrolled women without stated health problems who were in early menopause ([Obel 1993](#)) or were postmenopausal and aimed to assess the effects of HT on endometrial safety ([Ferenczy 2002](#); [Obel 1993](#)) and other clinical outcomes ([Greenspan 2005](#); [Tierney 2009](#)).

[WISDOM 2007](#) recruited women with no known major health problems from general practice registers in countries with free or low fee healthcare systems. Investigators designed recruitment to target older women first; as a result, median participant age was 63 years and few women in the younger age group were included when the study closed prematurely.

Studies of women with established medical conditions or a history of cancer

Six studies included women with established cardiovascular disease ([ERA 2000](#); [ESPRIT 2002](#); [EVTET 2000](#); [HERS 1998](#); [WAVE 2002](#); [WEST 2001](#)). [ERA 2000](#) and [WAVE 2002](#) included women who had coronary artery stenosis evident on angiogram. [HERS 1998](#) and [ESPRIT 2002](#) randomised women who had had a myocardial infarction or (in the case of [HERS 1998](#)) coronary artery surgery. [EVTET 2000](#) and [WEST 2001](#) included women who had had a thromboembolic (pulmonary embolism (PE) or deep vein thrombosis (DVT)) or cerebrovascular event (stroke or TIA). The largest of these six studies ([HERS 1998](#)) compared its cohort of women with a similar group of women presumed to have coronary heart disease, who were participants in a survey designed to produce nationally representative data: The [HERS 1998](#) cohort included significantly fewer smokers, women with hypertension and women with diabetes than the comparison group, but individuals were comparable with respect to blood pressure, body mass index, physical activity and cholesterol levels.

One study ([Mulnard 2000](#)) included women with Alzheimer's disease, and an older study ([Nachtigall 1979](#)) included women with a range of medical conditions such as diabetes, need for custodial care, arteriosclerosis and chronic neurological disorders: All participants in this study were hospitalised for the duration of the 10-year study.

One study enrolled women after surgery (including bilateral salpingo-oophorectomy) for early-stage endometrial cancer ([Barakat 2006](#)).

Interventions

The included studies used a wide variety of oestrogen-alone or oestrogen and progestogen combinations as interventions; some included more than one intervention arm, each with a different dose, formulation or route of HT. Most comparisons used a moderate dose of oestrogen (e.g. oestradiol 1 mg, conjugated equine oestrogen (CEE) 0.625 mg daily, transdermal oestradiol 0.05 mg twice weekly). [Nachtigall 1979](#) used a much higher dose than the other included studies, reflecting the fact that it was conducted many years earlier than the others.

The range of interventions used follows here.

Oestrogen-only HTs

These included the following.

1. Oestradiol (17-B oestradiol), an oestrogen derived from Mexican wild yam, 1 mg orally ([ELITE 2014](#); [EPAT 2001](#); [WEST 2001](#)).
2. Oestradiol valerate, which is a pro-drug for oestradiol (meaning that it is converted in the body into the active form); the dose used was 2 mg ([ESPRIT 2002](#)).
3. Transdermal oestradiol skin patches; doses used were 0.014 mg ([Yaffe 2006](#)) and 0.025 mg, 0.05 mg or 0.075 mg daily ([Notelovitz 2002](#)).
4. Intranasal 17-B oestradiol, delivered by a puff via each nostril once a day, at a dose of 0.15 mg or 0.3 mg daily ([Nielsen 2006](#)).
5. Conjugated equine oestrogen (CEE), a blend of equine oestrogens; 0.625 mg ([Barakat 2006](#); [ERA 2000](#); [Greenspan 2005](#); [Mulnard 2000](#); [PEPI 1995](#); [WAVE 2002](#); [WHI 1998](#) (oestrogen-only HT arm)) and 1.25 mg daily ([Mulnard 2000](#)). One study

(Barakat 2006) allowed doubling of the dose for women who were symptomatic. WISDOM 2007 also included an oestrogen-only arm, but the comparison group was taking combined therapy, and this comparison is not relevant to this review.

Most studies using oestrogen-only HT did not randomise women to this comparison unless they had had a hysterectomy (Greenspan 2005; Mulnard 2000; Nachtigall 1979; Notelovitz 2002; WAVE 2002; WEST 2001; WHI 1998 (oestrogen-only HT arm)).

Combined HT regimens

Combined regimens included one of the above types of oestrogen in combination with one of the following progestogens.

1. Medroxyprogesterone acetate (MPA), a synthetic progestogen structurally related to progesterone.
2. Dydrogesterone, a synthetic progestogen structurally related to progesterone.
3. Norethisterone (norethindrone), a synthetic progestogen structurally related to testosterone.
4. Micronised progesterone, a natural progestogen synthesised from plant sources and finely ground to improve its absorption.
5. Drosperinone, a synthetic progestogen structurally related to spironolactone.

Continuous combined regimens

These included the following.

1. CEE 0.625 mg with MPA 2.5 mg daily (EPHT 2006; ERA 2000; Greenspan 2005; HERS 1998; PEPI 1995; WAVE 2002; WHI 1998 (combined arm); WISDOM 2007).
2. CEE 2.5 mg with MPA 10 mg daily (Nachtigall 1979).
3. Oestradiol 2 mg with 1 mg norethisterone daily (EVTET 2000).

Combined sequential regimens

These included the following.

1. Oestradiol 1 mg daily with MPA 5 mg for 12 days once a year (WEST 2001).
2. Oestradiol 1 mg daily for 4 days, oestradiol 1 mg plus 0.35 mg norethindrone daily for 3 days each week (Tierney 2009).
3. Oestradiol 2 mg days 1 to 22, 1 mg days 22 to 28, with norethisterone 1 mg days 13 to 22 (Obel 1993).
4. Oestradiol 1 mg daily with dydrogesterone 5 mg or 10 mg days 14 to 28 (Ferenczy 2002).
5. Oestradiol 2 mg daily with 10 to 20 mg dydrogesterone days 14 to 28 (Ferenczy 2002).
6. Oestradiol 0.05 mg patch with cyclic micronised progesterone 200 mg daily for 12 days a month (KEEPS 2012).
7. CEE 0.425 mg daily with cyclic micronised progesterone 200 mg daily for 12 days a month (KEEPS 2012).
8. CEE 0.625 with MPA 10 mg days 1 to 12 (PEPI 1995).
9. CEE 0.625 mg with micronised progesterone 200 mg days 1 to 12 (PEPI 1995).
10. Oral oestradiol 1 mg daily, plus 40 mg cyclic micronised progesterone as 4% vaginal gel for 10 days per 30-day cycle for women with an intact uterus only (ELITE 2014).

The control arm of each study received placebo tablets, patches or nasal spray, as appropriate.

The duration of HT use varied, with the longest study lasting 10 years (Nachtigall 1979). Three studies reported outcomes after HT use for around 1 year (EVTET 2000; Mulnard 2000; WISDOM 2007); seven measured outcomes after 2 years (EPAT 2001; ESPRIT 2002; Ferenczy 2002; Notelovitz 2002; Obel 1993; Tierney 2009; Yaffe 2006), eight at around 3 years (Barakat 2006; EPHT 2006; ERA 2000; Greenspan 2005; PEPI 1995; WAVE 2002; WEST 2001) and 1 at 4 years (KEEPS 2012). HERS 1998 measured outcomes after 4.1 years and continued the study unblinded for 2.7 additional years. ELITE 2014 measured outcomes after 2.5 years and subsequently at 5 years of HT use.

Investigators planned that interventions in the WHI study would continue for 8.5 years, but both arms of the study were terminated early. WHI 1998 (combined HT arm) was stopped early owing to net harm. Researchers reported outcomes at 5.6 years and over 4 subsequent months of follow-up for primary and selected outcomes, incorporating events up to the date that participants were instructed to stop their study pills. WHI 1998 (oestrogen-only HT arm) was also stopped early when it was decided that the prospect of obtaining more precise evidence about effects of the intervention was unlikely to outweigh potential harms, although no predefined safety boundaries had been crossed. Investigators reported results in the oestrogen-only arm for a mean follow-up of 7.1 years for primary outcomes: Median time receiving treatment was 5.9 years in the intervention group and 5.8 years in the placebo group. Additional poststudy follow-up occurred in WHI 1998, as noted below.

Two other studies also closed prematurely in response to WHI 1998 findings (EPHT 2006; WISDOM 2007).

See [Characteristics of included studies](#).

Outcomes

The outcomes measured by individual studies varied according to study objectives. Major clinical events were not primary outcomes for several of these studies but were measured as adverse effects, for example, cardiovascular events or the incidence of cancer and fracture in the study population, or both. Eight studies used biological measures as their primary outcome (ELITE 2014; EPAT 2001; ERA 2000; KEEPS 2012; Notelovitz 2002; PEPI 1995; WAVE 2002; Yaffe 2006).

The largest study in the review (WHI 1998) was concerned mainly with the cardioprotective role of HT in relatively healthy women, and study authors reported cardiovascular clinical endpoints as the primary outcome. They designated invasive breast cancer as a primary adverse outcome and included the incidence of other cancers, fractures, gallbladder disease and death as secondary outcomes. Two other studies (EPHT 2006; WISDOM 2007) measured similar outcomes.

WHI 1998 also conducted a number of analyses not specified in the study protocol. Lung cancer was not a prespecified outcome but was investigated in both arms of the study in post hoc analyses, which included additional follow-up periods after the planned completion date of the study.

After the intervention phase of [WHI 1998](#) had been completed, investigators followed up major clinical outcomes in surviving participants (i.e. those who consented), comprising 78% of participants in the oestrogen-only arm and 83% in the combined HT arm. Median cumulative follow-up (intervention phase plus extended follow-up) was 13.2 years in the oestrogen-only arm (including median postintervention follow-up of 6.6 years) and 13 years in the combined HT group (including median postintervention follow-up of 6.6 years) ([Manson 2013](#)).

[WHI 1998](#) (WHIMS) comprised a large subset of older women from [WHI 1998](#) who were evaluated for probable dementia (the planned primary outcome) and for mild cognitive impairment (as a planned secondary outcome). Researchers also reported global cognitive function, although this was not a formally preplanned endpoint. [WHI 1998](#) (WHIMS) reported separate results for the two study arms and also pooled study results, but we did not include the pooled results in this review (see [Methods](#)).

Two smaller studies reported endometrial cancer as a primary outcome ([Barakat 2006](#); [Ferenczy 2002](#)), and two ([Obel 1993](#); [Tierney 2009](#)) reported as primary outcomes clinical events that were not of interest for this review, but researchers measured outcomes of interest as adverse events.

Five other studies were concerned with the effect of HT on established clinical disease. Four reported cardiovascular

outcomes: Primary outcomes were myocardial infarction or death ([ESPRIT 2002](#); [HERS 1998](#)), thromboembolism ([EVTET 2000](#)) and stroke ([WEST 2001](#)). The larger studies also measured a range of other major clinical events such as the incidence of cancer, fracture and gallbladder disease ([ESPRIT 2002](#); [HERS 1998](#)). One study reported the effect of HT on global cognitive function ([Greenspan 2005](#)) and one on progression of symptoms in women with Alzheimer's disease ([Mulnard 2000](#)); another study measured a wide range of clinical outcomes over a treatment period of 10 years with HT in women who were receiving long-term hospital care for a range of medical conditions ([Nachtigall 1979](#)).

Excluded studies

We excluded 42 studies from this review for the following reasons.

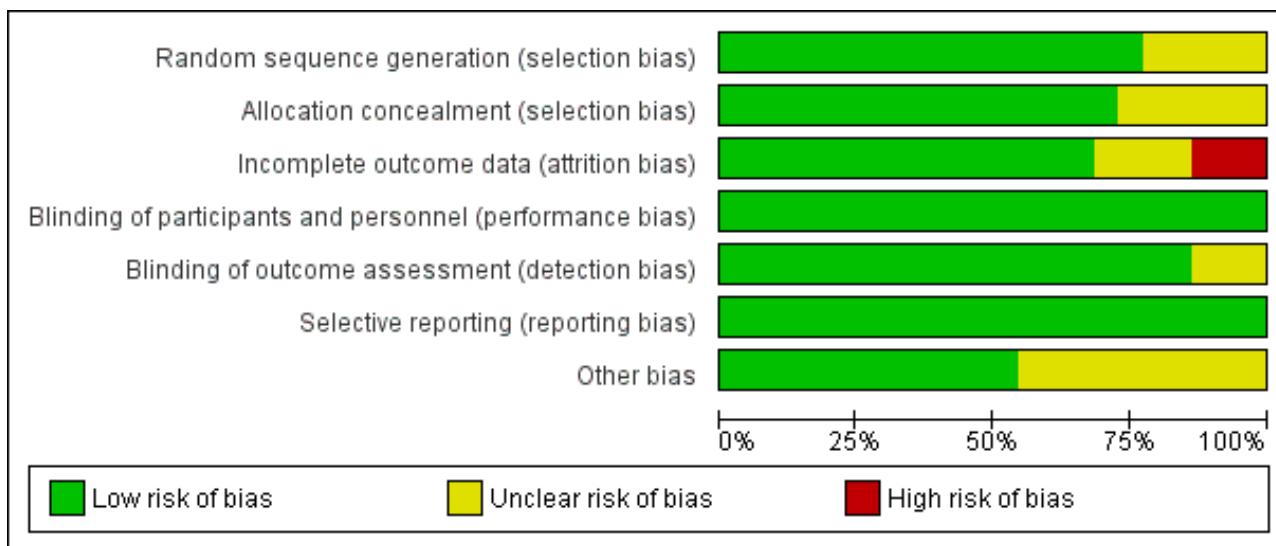
1. 29 reported no outcomes of interest for this review.
2. 5 were not double-blinded.
3. 4 used an intervention of less than 1 year's duration or reported only short-term (3-month) outcomes.
4. 3 did not include a placebo group.
5. 1 used a co-intervention in the HT group.

See [Excluded studies](#).

Risk of bias in included studies

See [Figure 1](#) and [Figure 3](#).

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Seventeen of the 22 studies described a satisfactory method of randomisation, which in all cases was computer generated. Sixteen described a satisfactory method of allocation concealment: In these studies, researchers entered information about an eligible participant, or they accomplished this via remote contact between the recruiting centre and the study coordinating centre or pharmacy. One of these studies ([EPHT 2006](#)) randomised women who expressed an interest in participating but did not open the randomisation envelope until their eligibility had

been checked and they had consented. Two studies described using computer-generated randomisation but did not provide details of the procedure for allocation to treatment ([EVTET 2000](#); [Mulnard 2000](#)). Three studies supplied no detailed information about randomisation nor allocation concealment ([Ferenczy 2002](#); [Nachtigall 1979](#); [Notelovitz 2002](#)).

We rated 17 studies as having low risk of bias related to sequence generation and 16 as having low risk of bias related to allocation concealment. We rated remaining studies as having unclear risk of bias in these domains.

Blinding

All studies described themselves as (at least) double-blinded. Eighteen studies explicitly stated that all participants, clinical staff and outcome assessors or research staff were blinded to treatment allocation, or they reported 'hard' outcomes unlikely to be influenced by blinding. In the WHI study, 331 women randomised to receive active treatment were unblinded and changed arms from **WHI 1998** (oestrogen-only HT arm) to **WHI 1998** (combined HT arm) according to a change in protocol. Three studies apparently blinded participants and clinical staff but did not explicitly state whether outcomes assessors were also blinded (**Mulnard 2000**; **Obel 1993**; **Tierney 2009**)

The larger studies described an unblinded mechanism to be used when required for management of adverse effects. **PEPI 1995** unblinded 39 women (4%) during the course of the study, 32 of whom were taking oestrogen-only HT. **WHI 1998** (combined HT arm) reported that during 5.6 years of follow-up, 3444 women in the combined HT group (40%) and 548 women in the placebo group (6%) were unblinded; whereas in **WHI 1998** (oestrogen-only HT arm), only 100 women in the active group (< 2%) and 83 in the placebo group (< 2%) were unblinded. **Nachtigall 1979** reported that 13 women in the HT group and 17 in the control group were unblinded. Two women were unblinded in **WISDOM 2007**. The other studies did not report such information.

One randomised blinded study (**HERS 1998**) completed 4.1 years of follow-up and was then extended for a further duration 2.7 years unblinded.

We rated all studies as having low risk of performance bias and 19 as having low risk of detection bias. We rated three studies as having unclear risk of detection bias.

Incomplete outcome data

For the purposes of this review, we defined losses to follow-up as participants for whom outcomes of interest were unknown (and who may or may not have had outcomes imputed in statistical analysis). We defined drop-outs as participants who stopped their allocated treatment (and in some cases changed to a different off-trial treatment) but had known clinical outcomes and were included in the analysis. Adherence to treatment refers to the number of tablets actually taken, which we often assessed by pill counts (**Table 1**). We defined intention to treat as analysis of all randomised participants in the groups to which they were randomised.

Drop-out rates were generally high, particularly in the active treatment groups, and they increased over time. In **WHI 1998** (combined HT arm), 42% of the active treatment group and 38% of the placebo group were no longer taking their allocated treatment at 5 years, and a further 10.7% of the placebo group had crossed to active therapy. In **WHI 1998** (oestrogen-only HT arm), 53% of participants overall were no longer taking their allocated treatment at 6.8 years, and a further 5.7% had initiated hormone use outside the study. See the **Characteristics of included studies** table and **Table 1** for details on drop-outs and non-adherence in other studies.

Losses to follow-up were low in most studies, with no women lost to follow-up in seven studies (**EPAT 2001**; **ERA 2000**; **ESPRIT 2002**; **EVTET 2000**; **Mulnard 2000**; **Nachtigall 1979**; **WEST 2001**), and 1% to 5.2% lost in five other studies, all of which were large and of long

duration (3 to 6.8 years) (**Greenspan 2005**; **HERS 1998**; **PEPI 1995**; **WAVE 2002**; **WHI 1998**). Only five women (0.01%) were lost to follow-up in **WISDOM 2007**. The Estonian study monitored outcomes by means of linkages to a national health insurance database and national cancer registry, and study authors stated that the probability of missing data in these databases was small (**EPHT 2006**). However, different publications for this study (**EPHT 2006**) reported slightly different numbers of randomised participants. In six smaller studies of 1 to 5 years' duration, a higher proportion of women (8.5% to 21%) were lost to follow-up (**ELITE 2014**; **KEEPS 2012**; **Notelovitz 2002**; **Obel 1993**; **Tierney 2009**; **Yaffe 2006**), and in **Ferenczy 2002**, results were unavailable for 34% of participants for the outcome of interest for this review. It was unclear whether any women were lost to follow-up in **Barakat 2006** (see **Description of studies**).

Fourteen of the included studies supplied sufficient data to permit an intention-to-treat (ITT) analysis, at least for all reported outcomes of interest for this review (**EPAT 2001**; **ERA 2000**; **ESPRIT 2002**; **EVTET 2000**; **Greenspan 2005**; **HERS 1998**; **KEEPS 2012**; **Mulnard 2000**; **Nachtigall 1979**; **Notelovitz 2002**; **WEST 2001**; **WHI 1998**; **WISDOM 2007**; **Yaffe 2006**), or such data were extractable, and a further two studies analysed more than 97% of participants by intention to treat (**PEPI 1995**; **WAVE 2002**). Five studies did not include all participants in an ITT analysis for outcomes of interest (**ELITE 2014**; **EVTET 2000**; **Ferenczy 2002**; **Obel 1993**; **Tierney 2009**). It was unclear whether one study used ITT analysis because investigators provided no description of participants other than those that were "eligible and assessable" (**Barakat 2006**), and one study had slightly differing participation rates across trial publications (**EPHT 2006**).

WHI 1998 (combined HT arm) and **WHI 1998** (WHISCA) continued follow-up beyond the planned study completion date (March 2005) for women who consented to continue follow-up. All women had already been instructed to stop taking their assigned study medication in July 2002. Seventeen per cent of surviving women in **WHI 1998** (combined HT arm) declined to provide re-consent, and their data were censored for the additional follow-up period. Baseline characteristics were similar in the two groups, and imputation analyses suggested that this loss to follow-up did not significantly influence study findings. Fifteen per cent of women in **WHI 1998** (WHISCA) declined to continue follow-up. The study extension phase ran from April 2005 to September 2010. **WHI 1998** (oestrogen-only HT arm) also conducted extended follow-up (in 78% of surviving participants) from April 2005 to September 2010; among women who provided additional consent, baseline characteristics were similar to those of the original randomised group.

We rated 16 studies as having low risk of attrition bias, four as having unclear risk and three as having high risk.

Selective reporting

All studies reported all expected outcomes, and we rated them as having low risk of selective reporting.

Other potential sources of bias

Eleven of the included studies had other potential sources of bias (**ELITE 2014**; **EPHT 2006**; **ERA 2000**; **Greenspan 2005**; **Mulnard 2000**; **Nachtigall 1979**; **Obel 1993**; **PEPI 1995**; **Tierney 2009**; **WAVE 2002**; **WHI 1998**); we rated them as having unclear risk of this bias. In most

cases, potential bias was related to baseline imbalance between participants in individual prognostic characteristics and did not appear likely to have a marked effect on outcomes. We rated the other studies as having low risk of bias in this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Combined continuous hormone therapy (HT) compared with placebo for postmenopausal women; **Summary of findings 2** Oestrogen-only hormone therapy (HT) compared with placebo for postmenopausal women

We present the results below. In most cases, details of effect measures are reported in the text only when results were statistically significant. For full results of all comparisons, see **Data and analyses**. See also **Summary of findings for the main comparison** and **Summary of findings 2**.

We grouped results as follows.

1. By outcome.

- We grouped outcomes such as death, cardiovascular events, cognitive measures and quality of life according to the clinical status of participant groups, in the following order: relatively healthy women, women with a history of cardiovascular disease, women hospitalised with chronic illness and women with dementia.
- For outcomes such as cancer, fracture and gallbladder disease, we grouped all participants together as 'all women'.

2. By intervention.

- Oestrogen-only HT.
- Combined continuous HT regimens.
- Combined sequential regimens.

Within these categories, we have grouped interventions according to the oestrogen dose used, with equivalence between doses based on the Australian Menopause Society guide to equivalent HT doses (**AMS 2016**), which classifies HT as low dose (e.g. oral oestradiol 1 mg), medium dose (e.g. oral oestradiol 2 mg, transdermal oestradiol 50 µg, conjugated equine oestrogen 0.065 mg) or higher dose (e.g. transdermal oestradiol 75 µg).

Meta-analysis

Although comparisons with similar oestrogen doses are grouped together, we pooled comparisons (meta-analysed) only if they used the same combination of oestrogen and progestogen for the same (or a similar) length of time. **WHI 1998** and **PEPI 1995** used the same HT regimen and reported several of the same clinical outcomes at 3 years, but in most cases, **PEPI 1995** reported no events in either arm. We combined three studies (**ERA 2000**; **HERS 1998**; **WAVE 2002**) for some 3-year (2.8 to 3.2) outcomes, but otherwise meta-analysis was inappropriate for most outcomes because the studies used different types or doses of oestrogen or progestogen, or both, and these do not necessarily have the same metabolic effects; or they used different durations of HT, which might have led to different effects as the result of trends over time.

Very few results were suitable for pooling; therefore, statistical heterogeneity was not a major issue in this review. One meta-analysis displayed statistically significant heterogeneity ($I^2 =$

66.2%), but it involved only two small studies with few events, and we attributed the heterogeneity to chance ([Analysis 2.21](#)).

Time points for reporting results

In some cases, we rounded up or down time points for reporting results, as follows.

- WHI 1998** (oestrogen-only HT arm) reported results after a mean follow-up of 7.1 or 7.9 years. Among women who consented (78% of those surviving), follow-up was extended (for a median of 6.6 years) after the predefined study termination date to achieve a cumulative median follow-up of 13.2 years. The median duration of active treatment in this arm of the study was 5.8 to 5.9 years ([LaCroix 2011](#)). We have reported results at mean or median follow-up points as reported by the study publications.
- WHI 1998** (combined HT arm) reported results after a mean of 5.6 years of active treatment (intervention phase) or at a mean of 7.9 years. The 7.9-year follow-up included 2.4 years of postintervention follow-up and continued up to the predefined study termination date (31 March 2005). Among women who consented (83% of those surviving), follow-up was extended after the predefined study termination date for a median of 6.6 years to achieve median cumulative follow-up of 13 years. This arm of the study also reported selected clinical outcomes for each year of follow-up: All women had been enrolled for at least 3.5 years at the time of the study publication, so we used these data to calculate outcomes on an ITT basis after 1, 2 and 3 years of use of HT, with all randomised participants inserted as the denominator ([Chlebowski 2009](#)). We have reported results at mean or median follow-up points as reported by the study publications.
- EPHT 2006** reported results for most outcomes at a mean follow-up of 3.43 years, with a range of 2 to 5 years. Results for quality of life were reported at a mean of 3.6 years. We have reported results in our tables as if all women underwent 3 years of follow-up.
- WISDOM 2007** reported results after a median follow-up of 11.9 months (range 7.1 to 19.6). We have reported results in our tables as if all women had undergone 1 year's follow-up.
- Barakat 2006** reported results after a median follow-up of 35.7 months. We have reported results in our tables as if all women had undergone 3 years of follow-up.
- HERS 1998** reported results from the blinded portion of the study after a mean follow-up of 4.1 years, which we mentioned above (see **Methods**). These results were presented as dichotomous data, and investigators reported selected clinical outcomes for each year of follow-up. All women had been enrolled for at least 3 years at the time of the report, so for this review, we have used these data to calculate outcomes on an ITT basis after 1, 2 and 3 years of HT use, with all randomised participants inserted as the denominator.

Results for outcomes of interest

We derived all of the statistically significant findings of this review from the two biggest studies - **HERS 1998** and **WHI 1998** - both of which reported adequate methods of allocation concealment, analysed all participants by intention to treat and reported small losses to follow-up (1% to 5.2%).

1. Death from any cause (total mortality)

Relevant comparisons

Seven studies ([ELITE 2014](#); [EPHT 2006](#); [EPAT 2001](#); [KEEPS 2012](#); [PEPI 1995](#); [WHI 1998](#); [WISDOM 2007](#)) with a total of eight different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from 1 year to nearly 8 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm), reported this outcome in healthy women.

Five studies of women with cardiovascular disease ([ERA 2000](#); [ESPRIT 2002](#); [HERS 1998](#); [WAVE 2002](#); [WEST 2001](#)) with a total of four different interventions, comprising comparisons of oestrogen-only HT and combined continuous HT versus placebo for varying durations from 2 to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), measured death from any cause.

Two other studies measured this outcome: one comparing oestrogen-only HT versus placebo in women who had undergone surgery for stage I or II endometrial cancer ([Barakat 2006](#)), and one ([Nachigall 1979](#)) comparing combined sequential HT versus placebo for 10 years in women hospitalised for chronic disease or because they required custodial care.

Results

Results of analysis show no statistically significant difference between HT and placebo for this outcome in any population group ([Analysis 1.1](#); [Analysis 1.2](#); [Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#); [Analysis 4.1](#); [Analysis 5.1](#)).

2. Cause-specific mortality

2.1 Death from coronary heart disease

Relevant comparisons

Four studies ([EPAT 2001](#); [Tierney 2009](#); [WHI 1998](#); [WISDOM 2007](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 8 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm), reported this outcome in relatively healthy women.

Five studies of women with cardiovascular disease ([ERA 2000](#); [ESPRIT 2002](#); [HERS 1998](#); [WAVE 2002](#); [WEST 2001](#)) with a total of four different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 2 to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), measured death from coronary heart disease.

In addition, the study comparing oestrogen-only HT versus placebo in women who had undergone surgery for stage I or II endometrial cancer measured this outcome ([Barakat 2006](#)).

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome in any population group ([Analysis 1.4](#); [Analysis 1.5](#); [Analysis 1.6](#); [Analysis 2.4](#); [Analysis 2.5](#); [Analysis 2.6](#); [Analysis 4.3](#)).

2.2 Death from stroke

Relevant comparisons

Four comparisons of relatively healthy women taking combined continuous HT for 1 year ([WISDOM 2007](#)) and for 5.6 years ([WHI 1998](#) (combined HT arm)), or taking oestrogen-only HT for 7.1 years ([WHI 1998](#) (oestrogen-only HT arm)) or taking combined sequential HT for 2 years ([Tierney 2009](#)), reported this outcome. One study of women with a history of stroke who were taking oestrogen-only HT (with annual progesterone for women who had a uterus) for 2.8 years ([WEST 2001](#)) also reported this outcome.

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome ([Analysis 1.7](#); [Analysis 1.9](#); [Analysis 1.8](#); [Analysis 2.8](#)).

2.3 Death from breast cancer

Relevant comparisons

One study of comparatively healthy women taking oestrogen-only HT for a median of 7.2 years ([WHI 1998](#) (oestrogen-only HT arm)) with postintervention follow-up for a median of 4.7 years reported this outcome, as did two studies of relatively healthy women taking combined continuous HT for 1 year ([WISDOM 2007](#)) and for 5.6 years ([WHI 1998](#)). Follow-up for breast cancer outcomes was continued for a mean total of 11 years among women in [WHI 1998](#) (combined HT arm) who agreed to continue follow-up after the planned study completion date ([Chlebowski 2010](#)).

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome at 1 or 5.6 years.

Among women taking oestrogen-only HT, after a median of 11.8 years (7.2 years' intervention plus postintervention follow-up), the death rate from breast cancer was lower in the HT arm (risk ratio (RR) 0.38, 95% confidence interval (CI) 0.15 to 0.98) ([WHI 1998](#) (oestrogen-only HT); [Analysis 1.12](#)).

At 11 years' follow-up, [WHI 1998](#) (combined HT arm) reported more deaths from breast cancer in the HT group than in the placebo group; this finding was of borderline statistical significance (RR 1.98, 95% CI 1.00 to 3.95; [Analysis 1.11](#)). Absolute risk of breast cancer increased from 1 per 1000 in the control group to 3 per 1000 (95% CI 1 to 6) in the HT group.

At 11 years' follow-up, researchers also found that significantly more deaths resulted from all causes after a breast cancer diagnosis in the combined HT group than in the placebo group (published hazard ratio (HR) 1.57, 95% CI 1.01 to 2.48; P = 0.045) ([Chlebowski 2010](#)).

2.4 Death from colorectal cancer

Relevant comparisons

Investigators reported this outcome in relatively healthy women in the oestrogen-alone group of [WHI 1998](#) after mean follow-up of 7.1 years, as well as in the [WHI 1998](#) (combined HT arm) at mean follow-up of 5.6 and 7.1 years. Researchers also reported on this after 11.6 years' follow-up, including a mean of 5.6 years' intervention plus postintervention follow-up after the study ended, in 83% of participants ([Simon 2012](#)).

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome ([Analysis 1.10](#); [Analysis 1.13](#)).

2.5 Death from endometrial cancer

Relevant comparisons

The study comparing oestrogen-only HT versus placebo in women who had undergone surgery for stage I or II endometrial cancer reported this outcome ([Barakat 2006](#)).

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome ([Analysis 4.2](#)).

2.6 Death from lung cancer

Relevant comparisons

[WHI 1998](#) reported this outcome in relatively healthy women in the oestrogen-only HT group in a post hoc analysis after mean follow-up of 7.9 years (including 8 months' follow-up post intervention) ([Chlebowski 2010b](#)), and in the combined HT arm of [WHI 1998](#) in a post hoc analysis after mean follow-up of 8 years (including 2.4 years' follow-up post intervention) ([Chlebowski 2009](#)). Study authors reported lung cancer overall, non-small cell lung cancer and small cell lung cancer separately. One much smaller study ([Tierney 2009](#)) reported this outcome in women taking combined sequential HT or placebo.

Results

Results of analysis show no statistically significant differences between HT and placebo for any of these outcomes among women in the oestrogen-only HT arm of [WHI 1998](#) ([Analysis 1.14](#)). However, in the combined HT arm of [WHI 1998](#), women in the intervention group were significantly more likely to die of lung cancer overall (RR 1.74, 95% CI 1.18 to 2.55), or of non-small cell lung cancer (RR 1.91, 95% CI 1.24 to 2.93), than women in the placebo arm ([Analysis 1.15](#)). Absolute risk of lung cancer increased from 5 per 1000 in the control group to 9 per 1000 (95% CI 6 to 13) in the HT group. This finding was independent of smoking status. The mortality rate for small cell lung cancer did not differ significantly between groups. Review authors noted no statistically significant findings in the combined sequential HT study ([Analysis 1.16](#)).

2.7 Death from any cancer

Relevant comparisons

Two studies of relatively healthy women taking continuous HT for 1 year ([WISDOM 2007](#)) and for 5.6 years ([WHI 1998](#) (combined HT arm)) and one study of women with cardiovascular disease taking combined continuous HT for 4.1 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)) reported this outcome.

Results

Results of analysis showed no statistically significant differences between HT and placebo for this outcome ([Analysis 1.17](#); [Analysis 2.9](#)).

3. Coronary events (myocardial infarction or cardiac death)

Relevant comparisons

Eight studies ([ELITE 2014](#); [EPAT 2001](#); [EPHT 2006](#); [KEEPS 2012](#); [PEPI 1995](#); [Tierney 2009](#); [WHI 1998](#), [WISDOM 2007](#)) with a total of nine different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from 1 year to over 7 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm) ([LaCroix 2011](#)) and to 13.2 years in the combined HT arm ([Manson 2013](#)), reported this outcome in relatively healthy women.

Six studies ([ERA 2000](#); [ESPRIT 2002](#); [EVTET 2000](#); [HERS 1998](#); [WAVE 2002](#); [WEST 2001](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from 2 to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), measured coronary events as an outcome in women with cardiovascular disease.

One other small study ([Nachtigall 1979](#)) measured this outcome and compared combined sequential HT versus placebo for 10 years in women hospitalised for chronic disease or because they required custodial care.

Results

[WHI 1998](#) (oestrogen-only HT arm) reported no statistically significant difference between the two groups for this outcome ([Analysis 1.18](#)). However, [WHI 1998](#) (combined HT arm) reported that relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) were at significantly higher risk of a coronary event after taking HT for 1, 2 and 3 years (at 1 year: RR 1.74 (95% CI 1.05 to 2.89); at 2 years: RR 1.49 (95% CI 1.05 to 2.12); at 3 years: RR 1.43 (95% CI 1.05 to 1.95)). At mean follow-up of 5.6 years, researchers noted no statistically significant differences between groups (RR 1.17, 95% CI 0.95 to 1.44), and they observed no differences between groups after extended follow-up to 13.2 years. [WISDOM 2007](#) and [EPHT 2006](#) reported data for this outcome at 1 year and at 3 years, respectively. Pooling these data with data from [WHI 1998](#) (combined HT arm) resulted in a risk ratio at 1 year of 1.89 (95% CI 1.15 to 3.10) and at 3 years of 1.45 (95% CI 1.07 to 1.98; [Analysis 1.19](#)). Absolute risk of a coronary event increased after 1 year from 2 per 1000 in the control group to 4 per 1000 (95% CI 3 to 7) in the HT group; after 2 years from 6 per 1000 in the control group to 9 per 1000 (95% CI 7 to 13) in the HT group; and after 4 years from 8 per 1000 in the control group to 11 per 1000 (95% CI 8 to 13) in the HT group.

No other studies found statistically significant differences between HT and placebo for this outcome ([Analysis 1.20](#); [Analysis 2.10](#); [Analysis 2.7](#); [Analysis 2.11](#); [Analysis 2.12](#); [Analysis 5.2](#)). [HERS 1998](#) reported results of borderline statistical significance at 1 year, suggesting increased risk for women with cardiovascular disease taking combined continuous therapy (RR 1.5, 95% CI 1.00 to 2.25; [Analysis 2.12](#)), and initial analysis of time trends in [HERS 1998](#) suggested a trend towards increased risk in the HT group that diminished over time. However, subsequent analysis based on the entire 6.8 years of follow-up (blinded and unblinded) showed no statistically significant variation in risk over time.

4. Stroke and transient ischaemic attack

4.1 Stroke

Relevant comparisons

Six studies ([EPAT 2001](#); [EPHT 2006](#); [KEEPS 2012](#); [PEPI 1995](#); [Tierney 2009](#); [WHI 1998](#)) with a total of seven different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 8 years, reported this outcome in relatively healthy women; [WHI 1998](#) (oestrogen-only arm) extended follow-up to 10.7 years, and [Manson 2013](#) extended follow-up to 13.2 years in the combined HT arm.

Five studies ([ESPRIT 2002](#); [EVTET 2000](#); [HERS 1998](#); [WAVE 2002](#); [WEST 2001](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), measured this outcome in women with cardiovascular disease.

Results

[WHI 1998](#) (oestrogen-only HT arm) reported a statistically significant increase in the incidence of stroke at 7.1 years' follow-up (RR 1.33, 95% CI 1.06 to 1.67; [Analysis 1.22](#)). Absolute risk of a stroke increased from 23 per 1000 in the control group to 32 per 1000 (95% CI 25 to 40) in the HT group. Study authors noted that the excess in the intervention arm was due to increased risk of ischaemic rather than haemorrhagic stroke, and that the excess risk became apparent after 4 years' follow-up ([Hendrix 2006](#)). However, increased risk was not maintained during extended follow-up (overall 10.7 years; RR 1.17, 95% CI 0.97 to 1.40) ([LaCroix 2011](#)). Although [WHI 1998](#) (combined HT arm) reported no statistically significant differences between groups in the incidence of stroke during the first 2 years of the study, women taking combined continuous HT were at significantly higher risk of stroke after taking HT for 3 or more years (at 3 years: RR 1.47, 95% CI 1.02 to 2.11; at a mean of 5.6 years: RR 1.39, 95% CI 1.09 to 1.77; at a mean of 7.9 years: RR 1.29, 95% CI 1.06 to 1.56). A statistically significant difference between groups was no longer evident at 13.2 years (RR 1.15, 99% CI 0.99 to 1.33). [EPHT 2006](#) also reported data for this outcome at 3 years; pooling these data with data from [WHI 1998](#) (combined HT arm) resulted in a risk ratio at 3 years of 1.46 (95% CI 1.02 to 2.09; [Analysis 1.23](#)). Absolute risk of a stroke increased at 3 years from 6 per 1000 in the control group to 8 per 1000 (95% CI 6 to 12) in the HT group; at 5.6 years from 14 per 1000 in the control group to 19 per 1000 (95% CI 15 to 24) in the HT group; and at 7.9 years from 21 per 1000 in the control group to 28 per 1000 (95% CI 23 to 34) in the HT group.

None of the other studies found any statistically significant differences between HT and placebo for this outcome ([Analysis 1.22](#); [Analysis 1.24](#); [Analysis 1.25](#); [Analysis 2.14](#); [Analysis 2.13](#); [Analysis 2.15](#)). As noted above, most of the relevant studies were small.

4.2 Transient ischaemic attack (TIA)

Relevant comparisons

Four studies ([ELITE 2014](#); [EPAT 2001](#); [PEPI 1995](#); [Tierney 2009](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined

sequential HT versus placebo, for 2 or 3 years, reported this outcome in relatively healthy women.

Three studies ([ESPRIT 2002](#); [HERS 1998](#); [WEST 2001](#)) of women with cardiovascular disease with a total of three different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 2 to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), also measured this outcome.

Results

Results of analysis show no statistically significant differences between HT and placebo for this outcome ([Analysis 1.26](#); [Analysis 1.27](#); [Analysis 2.16](#); [Analysis 2.17](#); [Analysis 2.18](#)).

4.3 Stroke or transient ischaemic attack

Relevant comparisons

One study of relatively healthy women ([WISDOM 2007](#)) taking combined continuous HT or placebo for a median of 1 year reported stroke or TIA as a combined outcome. Another study ([ERA 2000](#)) of women with known coronary disease taking oestrogen-only HT, combined continuous therapy or placebo also reported this combined outcome at 3.2 years' mean follow-up.

Results

Neither study found a statistically significant difference for this outcome between women taking HT and women taking placebo ([Analysis 1.29](#); [Analysis 2.20](#); [Analysis 2.19](#)).

5. Venous thromboembolism (pulmonary embolus or deep vein thrombosis)

Relevant comparisons

Six studies ([ELITE 2014](#); [EPAT 2001](#); [PEPI 1995](#); [Tierney 2009](#); [WHI 1998](#); [WISDOM 2007](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 8 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm), reported this outcome in relatively healthy women.

Five studies of women with cardiovascular disease ([ERA 2000](#); [ESPRIT 2002](#); [EVTET 2000](#); [HERS 1998](#); [WAVE 2002](#)) with a total of five different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 to 4 years, with unblinded follow-up to 6.8 years ([HERS 1998](#)), also measured venous thromboembolism.

One other small study ([Nachtingall 1979](#)) measured this outcome and compared combined sequential HT versus placebo for 10 years in women hospitalised for chronic disease or because they needed custodial care.

Results

[WHI 1998](#) (oestrogen-only HT arm) reported that relatively healthy women taking oestrogen-only HT (CEE 0.625 mg) were at higher risk of a thromboembolic event than women taking placebo. Risk was highest within the first 2 years and was statistically significant during this time period (RR 2.22, 95% CI 1.12 to 4.39). Absolute risk of an event increased from 2 per 1000 in the control group to 5

per 1000 (95% CI 2 to 10) in the HT group. At a mean follow-up of 7 years, risk was lower, but the intervention group was still at higher risk bordering on statistical significance (RR 1.32, 95% CI 1.00 to 1.74). The increased risk disappeared during extended follow-up (overall 10.7 years' follow-up: RR 1.05, 95% CI 0.84 to 1.31). When deep vein thrombosis was considered as a single outcome (without pulmonary embolism), the rate was significantly lower in the HT group during extended follow-up (RR 0.63, 95% CI 0.41 to 0.98), although the rate over the entire 10.7 years' intervention and extended follow-up did not differ significantly between the two groups (RR 1.04, 95% CI 0.84 to 1.29; [Analysis 1.30](#)).

WHI 1998 (combined HT arm) reported that relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) were at significantly higher risk of a thromboembolic event than women taking placebo; this applied at 1 to nearly 8 years' follow up (at 1 year: RR 3.59, 95% CI 1.95 to 6.61; at 2 years: RR 2.98, 95% CI 1.88 to 4.71; at 3 years: RR 2.54, 95% CI 1.73 to 3.72; at a mean of 5.6 years: RR 2.03, 95% CI 1.55 to 2.64; at a mean of 7.9 years: RR 1.65, 95% CI 1.32 to 2.05). Analysis of this comparison revealed a statistically significant time trend for diminishing risk of venous thromboembolism over time. **WISDOM 2007** also reported data for this outcome at 1 year; pooling these data with data from **WHI 1998** (oestrogen-only HT arm) resulted in a risk ratio at 1 year of 4.28 (95% CI 2.49 to 7.34) ([Analysis 1.32](#)). Absolute risk of an event increased at 1 year from 2 per 1000 in the control group to 7 per 1000 (95% CI 4 to 11) in the HT group; at 2 years from 3 per 1000 in the control group to 9 per 1000 (95% CI 6 to 14) in the HT group; and at 5.6 years from 10 per 1000 in the control group to 20 per 1000 (95% CI 15 to 26) in the HT group.

Similarly, in **HERS 1998**, women with cardiovascular disease who were taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) for 1 to 4 years were significantly more likely to experience a venous thromboembolism than women on placebo (at 1 year: RR 3.26, 95% CI 1.06 to 9.96; at 2 years: RR 3.51, 95% CI 1.42 to 8.66; at 3 years: RR 3.01, 95% CI 1.50 to 6.04; at a mean of 4.1 years: RR 2.62, 95% CI 1.39 to 4.94; [Analysis 2.22](#)). Absolute risk of an event increased at 1 year from 3 per 1000 in the control group to 9 per 1000 (95% CI 3 to 29) in the HT group; at 2 years from 4 per 1000 in the control group to 15 per 1000 (95% CI 6 to 38) in the HT group; and at 4.1 years from 9 per 1000 in the control group to 13 per 1000 (95% CI 6 to 28) in the HT group.

None of the other studies found any statistically significant differences between HT and placebo for this outcome ([Analysis 1.31](#); [Analysis 2.21](#); [Analysis 5.3](#)).

6. Breast cancer

Relevant comparisons

Nine studies (**ELITE 2014**; **EPAT 2001**; **EPHT 2006**; **Greenspan 2005**; **KEEPS 2012**; **Notelovitz 2002**; **PEPI 1995**; **WHI 1998**; **WISDOM 2007**) with a total of 11 different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 8 years, reported this outcome in relatively healthy women. **WHI 1998** (combined HT arm) extended follow-up beyond the planned completion date to achieve a mean 11-year follow-up for this outcome in the 85% of women who consented to stay in the study; **WHI 1998** (oestrogen-only arm) extended follow-up to a total of 10.7 years in the 78% of women who agreed to continue.

Four studies (**ERA 2000**; **ESPRIT 2002**; **HERS 1998**; **WAVE 2002**) with a total of four different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 2 to 4 years, with unblinded follow-up to 7.1 years (**HERS 1998**), measured this outcome in women with cardiovascular disease.

One other small study (**Nachtigall 1979**) measured this outcome and compared combined sequential HT versus placebo for 10 years in women hospitalised for chronic disease or because they required custodial care.

Results

WHI 1998 (oestrogen-only HT arm) reported a non-statistically significant decrease in risk of breast cancer at 7.1 years' follow-up among relatively healthy women taking oestrogen-only HT (CEE 0.625 mg) compared with women taking placebo (RR 0.79, 95% CI 0.61 to 1.01). Follow-up continued for a median of 5.8 years after the intervention phase. The overall cumulative breast cancer incidence over the 10.7 years' mean follow-up (median 11.8 years) showed a significantly lower rate in the HT group (RR 0.78, 95% CI 0.63 to 0.96). Absolute risk of breast cancer decreased over 10.7 years' follow-up from 37 per 1000 in the control group to 29 per 1000 (95% CI 23 to 35) in the HT group. The overall cumulative rate remained lower after a median of 13 years' follow-up (RR 0.80, 95% CI 0.65 to 0.97). Study authors noted that when event rates in the early and late postintervention periods were compared, hazard ratios (HRs) for breast cancer differed significantly ($P = 0.04$). The significant difference between groups in HR for breast cancer diminished over time and disappeared at approximately 4.5 years post intervention (**Chlebowski 2015a**).

WHI 1998 (combined HT arm) reported this outcome at yearly intervals. Results showed no statistically significant differences between groups in the incidence of breast cancer during the first 4 years of follow-up, but the HT group was at significantly higher risk of breast cancer after taking HT for 5 or more years (at a mean of 5.6 years' follow-up: RR 1.27, 95% CI 1.03 to 1.56; at a mean of 7.9 years' follow-up: RR 1.27, 95% CI 1.07 to 1.52). Absolute risk of breast cancer increased at 5.6 years' follow-up from 19 per 1000 in the control group to 23 per 1000 (95% CI 19 to 29) in the HT group; and at 7.9 years' follow-up from 26 per 1000 in the control group to 33 per 1000 (95% CI 28 to 40) in the HT group. Analysis in this arm of **WHI 1998** revealed a statistically significant trend for increasing breast cancer risk over time in the group taking HT. **WISDOM 2007** also reported data for this outcome at a median follow-up of 1 year. Pooling these data with data from **WHI 1998** (combined HT arm) resulted in significantly reduced risk of breast cancer at 1 year in the HT arm (RR 0.53, 95% CI 0.28 to 0.96). However, at a mean of 11 years' follow-up in **WHI 1998** (combined HT arm), the rate of invasive breast cancer was significantly higher in the HT arm (RR 1.25, 95% CI 1.08 to 1.45). Rates remained higher in the intervention arm at a median of 13.2 years' follow-up (RR 1.28, 95% CI 1.11 to 1.47) ([Analysis 6.3](#)). Breast cancers diagnosed in the HT group were of similar histology and stage to those diagnosed among controls but were more likely to be node positive ($P = 0.03$).

Results of analysis show no statistically significant differences between any other type of HT and placebo for this outcome, although (as noted above) relevant studies were small ([Analysis 6.1](#); [Analysis 6.2](#); [Analysis 6.3](#); [Analysis 6.4](#)).

7. Colorectal cancer

Relevant comparisons

Seven studies ([ELITE 2014](#); [EPAT 2001](#); [HERS 1998](#); [Greenspan 2005](#); [PEPI 1995](#); [Tierney 2009](#); [WHI 1998](#), [WISDOM 2007](#)) with a total of seven different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 8 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm), reported this outcome. Investigators also reported this outcome after extended follow-up in [WHI 1998](#) (combined HT arm) at 11.6 years ([Simon 2012](#)) and at 13.2 years ([Manson 2013](#)).

One other small study ([Nachtigall 1979](#)) measured this outcome and compared combined sequential HT versus placebo for 10 years in women hospitalised for chronic disease or because they required custodial care.

Results

[WHI 1998](#) (combined HT arm) reported no statistically significant differences in the incidence of colorectal cancer among relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) compared with women taking placebo, at 1 to 4 years' follow-up. However, women taking combined continuous HT had a significantly lower incidence of colon cancer at a mean follow up of 5.6 years (RR 0.64, 95% CI 0.44 to 0.91). Absolute risk of colorectal cancer decreased from 9 per 1000 in the control group to 6 per 1000 (95% CI 4 to 8) in the HT group. Rates tended to favour the HT group over extended follow-up: The difference was not statistically significant at 7.9 years (RR 0.76, 95% CI 0.57 to 1.01) nor at 13.2 years (RR 0.80, 95% CI 0.63 to 1.01) but did reach statistical significance at 11.6 years (RR 0.78, 95% CI 0.61 to 0.99).

Results of analysis show no statistically significant differences between any other type of HT and placebo for this outcome ([Analysis 6.6](#); [Analysis 6.7](#); [Analysis 6.8](#); [Analysis 6.9](#)).

8. Lung cancer

Relevant comparisons

[WHI 1998](#) (oestrogen-only arm) reported this outcome in relatively healthy women after a mean follow-up of 7.1 years; [WHI 1998](#) (combined HT arm) reported this outcome at 5.6 years and after extended follow-up at 7.9 years and 14 years.

Results

Results of analysis show no statistically significant differences between HT and placebo groups for this outcome ([Analysis 6.12](#); [Analysis 6.11](#); [Analysis 6.13](#)).

9. Endometrial cancer

Relevant comparisons

Nine studies ([EPAT 2001](#); [ESPRIT 2002](#); [Ferenczy 2002](#); [HERS 1998](#); [KEEPS 2012](#); [Nachtigall 1979](#); [Obel 1993](#); [PEPI 1995](#); [WHI 1998](#) (combined HT arm)) with a total of 13 different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo, for varying durations from 1 year to nearly 10 years, reported this outcome. [WHI 1998](#) (combined HT arm) also reported this outcome after extended follow-up, at 13.2 years. The study of

oestrogen-only HT versus placebo in women who had undergone surgery for stage I or II endometrial cancer ([Barakat 2006](#)) measured recurrent endometrial cancer. In comparisons of oestrogen-only HT versus placebo ([EPAT 2001](#); [ESPRIT 2002](#); [PEPI 1995](#)), all women with a uterus were monitored closely for endometrial hyperplasia, and two studies specified that study medications were withdrawn if atypical hyperplasia was detected ([ESPRIT 2002](#); [PEPI 1995](#)).

Results

At 13 years' median follow-up, rates of endometrial cancer were lower in the combined HT group (RR 0.66, 95% CI 0.48 to 0.90) in [WHI 1998](#).

Results of analysis showed no other statistically significant differences between HT and placebo for this outcome ([Analysis 6.14](#); [Analysis 6.15](#); [Analysis 6.14](#); [Analysis 6.16](#)), and no statistically significant differences between groups in rates of recurrent endometrial cancer ([Analysis 6.17](#)). One study ([Obel 1993](#)) reported no events.

10. Ovarian cancer

Relevant comparisons

[WHI 1998](#) (combined HT arm), which used combined continuous CEE 0.625 mg + MPA 2.5 mg at 5.6 years' mean follow-up and again after extended follow-up, at 13.2 years ([Manson 2013](#)), reported ovarian cancer incidence, and [ELITE 2014](#), which utilised oestrogen with or without sequential progesterone vaginal gel, reported a single event.

Results

Results of analysis showed no statistically significant differences between groups for this outcome ([Analysis 6.18](#)).

11. Gallbladder disease

Relevant comparisons

Four studies ([ERA 2000](#); [HERS 1998](#); [PEPI 1995](#); [WHI 1998](#)), which compared oestrogen-only HT, combined continuous HT and sequential combined HT versus placebo for 3 to over 7 years, reported gallbladder disease requiring surgery. For this outcome, the two largest studies stated that they excluded from analysis women who had had their gallbladder removed ([HERS 1998](#)), who reported a history of gallbladder disease, or both ([WHI 1998](#)).

Results

Meta-analysis of the three studies comparing oestrogen-only HT versus placebo for the outcome of gallbladder disease requiring surgery ([ERA 2000](#); [PEPI 1995](#); [WHI 1998](#)) showed a statistically significant increase in risk in the HT group (RR 1.75, 95% CI 1.40 to 2.19); these studies had a mean follow-up ranging from 3 to 7.1 years. Absolute risk of an event increased from 26 per 1000 in the control group to 45 per 1000 (95% CI 36 to 57) in the HT group. Meta-analysis of the four studies comparing combined continuous HT versus placebo ([ERA 2000](#); [HERS 1998](#); [PEPI 1995](#); [WHI 1998](#)) showed significantly increased risk in the HT group (RR 1.55, 95% CI 1.29 to 1.86); these studies had a mean follow-up ranging from 3 to 5.6 years. Absolute risk of an event increased from 27 per 1000 in the control group to 47 per 1000 (95% CI 38 to 60) in the HT group. Although these studies had differing lengths of follow-up, review authors noted no statistical heterogeneity in either meta-analysis. Similarly, during unblinded follow-up, [HERS](#)

1998 reported an increase in events in the HT group that reached borderline statistical significance (RR 1.63, 95% CI 1.00 to 2.70; [Analysis 6.20](#); [Analysis 6.21](#); [Analysis 6.22](#)). WHI 1998 investigators reported that hazard estimates for risk in active and placebo groups started to diverge during the first year of follow-up, with the oestrogen group separating earlier than the combined continuous HT group.

12. Fractures

12.1 Hip fracture

Relevant comparisons

Five studies, which compared combined continuous HT ([HERS 1998](#); [WHI 1998](#); [WISDOM 2007](#)), combined sequential HT ([Tierney 2009](#); [WEST 2001](#)) and oestrogen-only HT ([WEST 2001](#); [WHI 1998](#)) versus placebo for between 1 and 7.9 years, with extended follow-up to 10.7 years in [WHI 1998](#) (oestrogen-only arm), and with extended follow-up to 13.2 years in both arms of [WHI 1998](#), reported the incidence of hip fracture.

Results

Both arms of [WHI 1998](#) found a statistically significant reduction in the risk of hip fracture for women taking HT. [WHI 1998](#) (oestrogen-only HT arm) reported a statistically significant reduction in the risk of hip fracture for women taking HT (CEE 0.625 mg) at 7.1 years' mean follow-up (RR 0.64, 95% CI 0.45 to 0.93; [Analysis 6.23](#)). Absolute risk of a hip fracture decreased from 14 per 1000 in the control group to 9 per 1000 (95% CI 6 to 13) in the HT group. Benefit derived from HT was not maintained during extended follow-up (to 13.2 years). [WHI 1998](#) (combined HT arm) reported this outcome at yearly intervals and found no statistically significant differences in the incidence of hip fracture during the first 4 years' follow-up, but at 5.6 years' mean follow-up, reduction in the risk of hip fracture among women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) was statistically significant (RR 0.68, 95% CI 0.48 to 0.97; [Analysis 6.25](#)). Absolute risk of hip fracture decreased from 9 per 1000 in the control group to 6 per 1000 (95% CI 4 to 9) in the HT group. This risk remained significantly lower in the HT group at mean follow-up of 7.9 years (RR 0.77, 95% CI 0.60 to 0.99) and 13.2 years (RR 0.82, 95% CI 0.69 to 0.97).

However, [HERS 1998](#) found no statistically significant differences between combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) and placebo for this outcome, and the unblinded extension of this study reported a statistically significantly *increased* risk in the group taking HT from years 4.1 to 6.8 (post randomisation) (RR 2.10, 95% CI 1.06 to 4.16; [Analysis 6.25](#)).

Other studies found no statistically significant differences between groups ([Analysis 6.24](#); [Analysis 6.26](#)).

12.2 Clinical vertebral fractures

Relevant comparisons

[WHI 1998](#) (oestrogen-only HT arm) reported the incidence of vertebral fracture at follow-up of 7.1 years. Two studies of combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) versus placebo ([HERS 1998](#); [WHI 1998](#) (combined HT arm)) also reported the incidence of vertebral fracture at follow-up from 4 to nearly 8 years.

Results

At a mean of 7.1 years' follow-up, [WHI 1998](#) (oestrogen-only HT arm) reported significantly fewer fractures in the oestrogen-only HT group (CEE 0.625 mg) than in the placebo group (RR 0.64, 95% CI 0.44 to 0.94; [Analysis 6.27](#)). Absolute risk of a clinical vertebral fracture decreased from 13 per 1000 in the control group to 8 per 1000 (95% CI 6 to 12) in the HT group. Similarly, at a mean of 5.6 years' follow-up, [WHI 1998](#) (combined HT arm) reported significantly fewer fractures in the HT group than in the placebo group (RR 0.68, 95% CI 0.48 to 0.97; [Analysis 6.28](#)). Absolute risk of a clinical vertebral fracture decreased from 10 per 1000 in the control group to 7 per 1000 (95% CI 5 to 10) in the HT group. At a mean of 7.9 years' follow-up, [WHI 1998](#) (combined HT arm) no longer observed significant differences between groups. [HERS 1998](#) found no significant differences between groups during follow-up.

12.3 Any fractures

Relevant comparisons

Nine studies ([EPHT 2006](#); [ERA 2000](#); [ESPRIT 2002](#); [Greenspan 2005](#); [HERS 1998](#); [Tierney 2009](#); [WEST 2001](#); [WHI 1998](#); [WISDOM 2007](#)) comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for 1 to nearly 8 years reported the incidence of any fracture.

Results

Both arms of [WHI 1998](#) showed a statistically significant reduction in the risk of any fracture for women taking HT. Investigators reported this at 5.6 and 7.9 years' mean follow-up in women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) (at 5.6 years: RR 0.78, 95% CI 0.71 to 0.86; at 7.9 years: RR 0.82, 95% CI 0.76 to 0.89) and at 7.1 years' mean follow-up in women taking oestrogen-only HT (CEE 0.625 mg) (RR 0.73, 95% CI 0.65 to 0.80) ([Analysis 6.30](#); [Analysis 6.32](#)). At 5.6 years, in [WHI 1998](#) (combined HT arm), absolute risk of any fracture decreased from 111 per 1000 in the control group to 86 per 1000 (95% CI 79 to 94) in the HT group, and in [WHI 1998](#) (oestrogen-only HT arm) at 7.1 years, absolute risk of any fracture decreased from 140 per 1000 in the control group to 102 per 1000 (95% CI 91 to 112) in the HT group. None of the other studies found any statistically significant differences between HT and placebo for this outcome ([Analysis 6.29](#); [Analysis 6.31](#); [Analysis 6.33](#)).

13. Cognitive function

13.1 Global cognitive function

Relevant comparisons

Five studies, which compared low-dose oestrogen patches versus placebo for 2 years ([Yaffe 2006](#)) and combined continuous CEE 0.625 mg with or without MPA 2.5 mg versus placebo for 3 years ([Greenspan 2005](#)), oestradiol 1 mg daily with or without intermittent vaginal progesterone gel with follow-up at 2.5 and 5 years ([ELITE 2014](#)), 0.45 mg oral or 0.05 mg transdermal oestrogen with intermittent progesterone 200 mg versus placebo for 4 years ([KEEPs 2012](#)), oestrogen-only HT versus placebo for a mean of 5.6 years ([WHI 1998](#) (WHIMS)) and continuous CEE 0.625 mg + MPA 2.5 mg versus placebo for a mean of 4.2 years ([WHI 1998](#) (WHIMS)), reported this outcome. Researchers measured global cognitive function using a cognitive screening test known as the Modified Mini-Mental State Examination (3MSE), on which a higher score reflects better cognitive functioning. [KEEPs 2012](#) included

women 42 to 58 years of age at randomisation, [WHI 1998](#) (WHIMS) included only women over 65 years of age and [Yaffe 2006](#) included only women over 60 years of age.

Results

Over 2 years' follow-up in [Yaffe 2006](#), 3 years' in [Greenspan 2005](#), 4 years' in and 2.5 years' or 5 years' in [ELITE 2014](#), investigators noted no significant difference in cognitive function between intervention and placebo groups. Nor did they observe any difference in the effect of treatment when women in [Yaffe 2006](#) were stratified according to cognitive status at baseline ($3MSE \leq 90$ or > 90) ([Analysis 1.34; Table 2](#)). Investigators in [ELITE 2014](#) subgrouped comparisons according to when oestradiol was initiated (within 6 years of menopause vs 10 or more years after menopause). Study results showed no evidence of differences between the two subgroups in the effect of HT on cognition at 2.5 years.

In both treatment groups and in both placebo groups of [WHI 1998](#) (WHIMS), mean 3MSE scores increased from baseline and continued to increase for 3 to 5 years before they started to decline. Results showed a pattern of higher increases from baseline in 3MSE scores in the placebo groups, which emerged after 1 to 2 years and were maintained throughout the study. The mean difference between groups in 3MSE score changes was of borderline statistical significance in both arms of the study, with results favouring the placebo group; however, in both cases, the lower boundary of the confidence interval was zero (oestrogen-only HT arm: weighted mean difference (WMD) -0.25, 95% CI -0.52 to 0.00; combined HT arm: WMD -0.18, 95% CI -0.35 to 0.00) ([Analysis 1.34](#)).

In the [WHI 1998](#) (WHIMS) combined HT arm, a decline of 10 points or more in 3MSE scores (which represents > 2 standard deviations from baseline mean scores) was significantly more likely to occur among women in the active treatment group (RR 1.57, 95% CI 1.10 to 2.24; [Analysis 1.31](#)). Study results showed the same trend in the oestrogen-only HT group, but this finding was not of statistical significance.

13.2 Probable dementia

Relevant comparisons

[WHI 1998](#) (WHIMS), which included only women over 65 years of age and compared oestrogen-only HT (CEE 0.625 mg) versus placebo for a mean of 5.6 years, and combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) versus placebo for a mean of 4.2 years, reported this outcome.

Results

In the oestrogen-only HT arm, researchers noted no statistically significant differences between groups. In the combined HT arm, the incidence of probable dementia was significantly higher in the group taking combined continuous HT than in the placebo group (RR 1.97, 95% CI 1.16 to 3.33). At 4.2 years, absolute risk of probable dementia increased from 9 per 1000 in the control group to 18 per 1000 (95% CI 11 to 30) in the HT group ([Analysis 1.35](#)).

13.3 Change in dementia status

Relevant comparisons

One small study ([Mulnard 2000](#)) included women with mild to moderate Alzheimer's disease. Researchers compared unopposed oestrogen for 1 year versus placebo and examined the primary

outcome of change in overall status with relation to Alzheimer's disease, as measured by the Clinical Global Impression of Change Scale.

Results

Results of analysis show no statistically significant differences between groups ([Analysis 3.1](#)).

Other analyses

Studies included in any one analysis were insufficient to allow construction of a funnel plot.

Use of a random-effects model had no material effect on any analyses. Studies in any one analysis were insufficient to permit sensitivity analysis by study risk of bias. Nor did any analyses include studies with marked clinical differences.

DISCUSSION

Summary of main results

Cardiovascular disease

No evidence indicates that hormone therapy (HT) has a role in the treatment or prevention of cardiovascular disease. On the contrary, HT significantly increases the incidence of stroke and venous thromboembolism, and combined continuous HT also significantly increases the risk of coronary events (myocardial infarction or cardiac death). Oestrogen-only HT does not appear to have any statistically significant effect (positive or negative) on coronary disease.

An increase in the risk of coronary events and in venous thromboembolism was evident during the first year of treatment among women taking combined continuous HT in both [HERS 1998](#) and [WHI 1998](#). Although a significant trend in both arms of [WHI 1998](#) and in the blinded phase of [HERS 1998](#) showed diminution of cardiovascular risk in the HT group over time, subsequent analysis of [HERS 1998](#) data, which included both blinded and unblinded follow-up, revealed no statistically significant variation in risk over time. [WHI 1998](#) investigators suggest that the apparent decline in cardiovascular risk in later years may be due to an acceleration of events during earlier years among susceptible women in the HT group, and they point out that with longer duration of treatment, the risk of breast cancer is increased.

[WHI 1998](#) (combined HT arm) conducted prespecified subgroup analyses to evaluate whether any clinical characteristics of the study population might plausibly modulate the coronary effects of HT. Variables included age, time since menopause, presence or absence of vasomotor symptoms, prior hormone use, coronary heart disease (CHD) risk factor status and presence or absence of preexisting cardiovascular disease. However, none of these variables significantly affected results.

Among women taking combined HT in [WHI 1998](#), those who had factor V Leiden mutation (a blood coagulation disorder) were at higher risk of venous thromboembolism ([Cushman 2004](#)). Statistical power was insufficient to allow investigators to determine whether significant excess risk was associated with a history of venous thromboembolism (among women taking combined HT). The incidence of thromboembolism was higher among older and obese women, although this was related to their

higher baseline risk of an event, and their risk ratio did not differ from that of other women taking combined HT.

It has been suggested that vascular effects of HT may differ according to a woman's age or time since onset of menopause. Thus oestrogen may counteract the early stages of atherosclerosis in recently menopausal women by inhibiting lipid deposits within the endothelium. However, HT may have adverse effects on more advanced disease, by facilitating an increase in enzymes that tend to disrupt atherosclerotic lesions, and by encouraging clot formation (Manson 2013; Reslan 2012). Research findings on the effect of HT in early menopause on intermediate outcomes of CVD are variable (ELITE 2014; KEEPS 2012), and research findings on this topic are continuing (Manson 2015).

Breast cancer

In WHI 1998 (combined HT arm), breast cancer rates in the HT group were initially lower than in the placebo group, and when WHI 1998 and WISDOM 2007 data were combined, at 1 year's follow-up, the difference reached statistical significance, favouring the intervention group. However, by the fourth year of use, more events occurred in the HT group, and a statistically significant trend showed increasing risk over time. At a mean of 11 years' follow-up in WHI 1998, women in the combined HT group had a significantly higher rate of invasive breast cancer than controls, and longer follow-up (to a median of 13.2 years) showed no evidence of attenuation of risk (Chlebowski 2015a). At 11 years, the trend toward a higher rate of death from breast cancer approached statistical significance (Chlebowski 2010). This long-term increase in risk was apparent despite evidence that the risk of breast cancer associated with combined HT declined markedly over the first 2 years after discontinuation of hormones (Chlebowski 2009a).

WHi 1998 investigators commented that breast cancers in the combined HT group were diagnosed at a similar grade but at a more advanced stage and suggested that combined HT may stimulate breast cancer growth while delaying diagnosis. Evidence shows that combined HT increases the frequency of abnormal mammograms and indications for breast biopsy but compromises the diagnostic performance of both of these tests (Chlebowski 2008). These factors would account for the lower incidence of breast cancer among women taking combined therapy during the first 2 years in WHI 1998. Subgroup analyses of prior hormone use in WHI 1998 revealed that the cumulative incidence of breast cancer over time in women taking combined HT increased at a greater rate than in women taking placebo after about 3 years for prior hormone users and after about 5 years for women with no prior use. Interference with mammography precluded the possibility of defining with any reliability a time frame for the safe use of combined HT (Anderson 2006).

WHi 1998 reported a decrease in the risk of breast cancer in the unopposed oestrogen arm of the trial, which reached statistical significance when investigators took into account the entire 10.7 years of intervention and extended follow-up. Cumulative event rates still differed significantly between groups over 13 years' follow-up, and risk of death from breast cancer was lower in the HT group at nearly 12 years. Comparison of hazard ratios during early and late postintervention periods showed that lower risk of breast cancer in the oestrogen arm persisted for about 4.5 years after the intervention was provided, at which point a significant difference between the interventions was no longer evident (Chlebowski

2015a; Chlebowski 2015b). Subgroup analyses showed significantly fewer early cancers and significantly fewer ductal carcinomas in the intervention group, although the incidence of lobular tumours did not differ significantly. Results showed that the reduction in breast cancer risk was concentrated in women without benign breast disease ($P = 0.01$) or a first-degree family history of breast cancer ($P = 0.02$) (Anderson 2012). Oestrogen-only HT appears to increase the number of women needing repeat mammography or breast biopsy but (in contrast to combined HT) does not appear to substantially compromise breast cancer detection (Chlebowski 2010a).

WHi 1998 researchers stated that differences between participants across the two arms of the study did not explain differences in breast cancer incidence and suggested that increased risk in the combined group might be due to progestogen. Similar trends in other studies (Beral 2003; HERs 1998) support this theory. A nested case-control study comparing pair-matched controls of women who developed breast cancer in either arm of WHI 1998 (Zhao 2014) suggested that post-treatment changes in serum oestrogens and concentrations of sex hormone-binding globulin, or changes in the association of such concentrations with disease risk, might explain both the increased breast cancer risk noted with combined HT and the reduction in risk seen with unopposed oestrogen. It has been observed that exposure to oestrogen after a sustained period of oestrogen deprivation reduces the risk of breast cancer (Jordan 2015; Obiorah 2013).

Colorectal cancer

The significantly reduced incidence of colorectal cancer in women taking combined continuous HT in WHI 1998 was offset by the finding that colorectal cancers diagnosed in such women tended to be more advanced, with greater likelihood of lymphatic or metastatic involvement. Moreover, the reduced incidence in the HT group did not lead to a reduced death rate from colorectal cancer over extended follow-up (7.1 years), although investigators noted that an even longer period of follow-up might be required to observe a mortality benefit from a reduction in the incidence of small, localised cancers. Women taking oestrogen-only HT in WHI 1998 did not have a reduced incidence of or death rate from colorectal cancer over 7 years' follow-up nor during extended follow-up to 10.7 years. Overall, no strong evidence suggests a clinically meaningful reduction in colorectal cancer rates with oestrogen-alone or oestrogen plus progestin. Findings in the WHI observational study supported this conclusion (Prentice 2009).

Lung cancer

Post hoc analysis of WHI 1998 data revealed that combined HT did not significantly increase the incidence of lung cancer over 8 years' follow-up but did increase mortality from lung cancer, independent of smoking status. Study authors (Chlebowski 2009) suggested that this might be so because combined HT stimulates the growth of preexisting small cell lung cancers.

Gynaecological cancers

None of the included studies showed an increase in the incidence of endometrial cancer in the group taking HT. Three studies randomised women with a uterus to oestrogen-only HT (EPAT 2001; ESPRiT 2002; PEPI 1995). As endometrial cancer is well documented as an adverse effect of unopposed oestrogen (Kurman 1985), these women were closely monitored for atypical endometrial hyperplasia and received treatment (and discontinuation of study

medications) if it was detected. [PEPI 1995](#) reported that women in the oestrogen-only HT group were significantly more likely to develop atypical endometrial hyperplasia than women in the placebo group, whereas women in the combined HT groups in the same study showed no increased risk of hyperplasia. After more than 13 years' extended follow-up, rates of endometrial cancer were lower in the combined HT group in [WHI 1998](#).

The study of oestrogen-only therapy in women who had undergone surgery for stage I or II endometrial cancer was underpowered owing to early discontinuation and could not conclusively refute or support the safety of this therapy with regard to risk of recurrence. Study authors note that recurrence rates were low, at 1.9% in the placebo group and 2.3% in the intervention group ([Barakat 2006](#)).

Results showed a trend towards increased risk of ovarian cancer in [WHI 1998](#) (combined HT arm), which did not reach statistical significance ([Anderson 2003](#)). As noted above, a systematic review of (mainly) observational studies ([Greiser 2006](#)) suggests that both oestrogen-only and combined therapy may be associated with increased risk of ovarian cancer.

A randomised study with 4-year follow-up of 130 women with a history of ovarian cancer ([Guidozzi 1999](#)) found that oestrogen-only hormone therapy did not negatively affect disease-free or overall survival time compared with no hormone therapy. A similar randomised study ([AHT 2015](#)) showed that women with severe menopausal symptoms after ovarian cancer who took HT (of varying types, according to consultant preference) had improved overall and relapse-free survival compared with controls not taking HT. The present systematic review did not include these studies because they lacked a placebo control group.

The apparent reduction in risk of endometrial cancer associated with combined HT is offset by the suggestion of increased risk of ovarian cancer ([Manson 2013](#)).

Fractures

Evidence on HT and fractures is not consistent. [WHI 1998](#) found a significantly reduced risk of fractures in women taking combined continuous HT or oestrogen-only HT over nearly 8 years' follow-up, but [HERS 1998](#) reported no benefit for women on continuous combined HT. Moreover, unblinded continuation of [HERS 1998](#) revealed a significantly *increased* risk of hip fracture among such women. Study authors attributed this finding to chance, noting that the effect was considerably smaller in the as-treated analysis, and that such a finding lacks biological plausibility ([Hulley 2004](#)). [WHI 1998](#) (combined HT arm) investigators tested the hypothesis that the beneficial effect of HT on fracture incidence differed according to fracture risk factors. They found that the reduction in risk provided by HT was no greater in women at high risk of fracture ([Cauley 2003](#)). However, [WHI 1998](#) excluded women with severe osteoporosis and did not routinely collect bone mineral density; thus the benefits of HT may outweigh the risks for some women with severe osteoporosis. Reduced risk of hip fracture associated with HT did not persist in the extended follow-up phase of [WHI 1998](#) (oestrogen-only HT).

Our analyses of hip fracture may have had insufficient power to reach conclusive findings. The risk of hip fracture rises steeply from the age of about 60 years but is still under 0.5% among women in the UK 65 to 69 years of age ([Banks 2009](#)).

Most women who need treatment for low bone mineral density require lifelong therapy, but the highest risk of cardiovascular events with combined HT occurs during the first year of use. Overall, although HT is considered effective for prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable ([Cranney 2002](#); [NIH 2004](#)).

Cognitive outcomes

[WHI 1998](#) (WHIMS) found that neither combined HT nor oestrogen-only HT improved global cognitive function in women over 65 years of age. Improvement in global cognitive function (Modified Mini-Mental State Examination (3MSE) scores) that occurred in all participant groups over the first few years of WHIMS was attributed to a learning effect resulting from repeated administration of cognitive tests ([Espeland 2004](#)). The difference in mean scores between active therapy and placebo groups was of borderline statistical significance and consistently favoured placebo groups, although the difference was too small to be clinically meaningful. However, a marked decrease in 3MSE scores (defined as > 2 standard deviations from the baseline mean) was more frequent in the active treatment groups, and this trend reached statistical significance in the combined HT group. Moreover, in both arms, HT had greater detrimental effects in women whose baseline 3MSE scores were lowest ([Espeland 2004](#)).

Similarly, for the outcome of probable dementia, a negative trend in both active treatment groups reached statistical significance in the combined HT group. Evidence of increased risk in this group began to appear as early as 1 year after randomisation and persisted over 5 years' follow-up. The overall risk of dementia in women taking combined HT was twice that in women in the corresponding placebo group. Investigators noted that the absolute risk of dementia remained relatively small, at 45 per 10,000 postmenopausal women over 65 years of age who took combined HT for 1 year ([Shumaker 2004](#)).

These findings were unexpected and contrast sharply with findings reported in earlier research. [WHI 1998](#) (WHIMS) investigators suggested that this might be due to the healthy user bias seen in observational studies (whereby HT users had a better prognosis at baseline than the control groups), to the differential effects of HT on specific domains of cognition not measured individually by 3MSE, or both. Alternatively, they suggested that HT might need to be initiated during a critical period, such as menopause, to protect cognitive function at a later age. The mean age of the WHIMS population was 71 years, and the study could not address this theory, although previous users of HT in WHIMS did not have higher scores ([Espeland 2004](#)). Moreover, results of extended follow-up in [WHI 1998](#) (WHISCA) show no evidence of any benefit in domain-specific cognitive function from oestrogen-alone or combined HT.

A post hoc comparison of global cognitive function among younger women in [WHI 1998](#) ([Espeland 2013](#); [Vaughan 2013](#)) included women randomised to either active arm of [WHI 1998](#) (CEE or combined HT) versus women in the placebo arm. Scores were similar in the two groups ($P = 0.66$). The study included 1376 women 50 to 55 years of age when randomised for [WHI 1998](#). Cognitive testing was conducted an average of 7.2 years following trial completion, when women had a mean age of 67.2 years, and was repeated 1 year later. Study investigators concluded that "CEE-based therapies produced no overall sustained benefit or risk to

cognitive function when administered to postmenopausal women aged 50–55 years". However, among 2880 women who had enrolled for [WHi 1998](#) at the age of 65 to 79 years, long-term decrements in global cognitive function were noted in the HT groups (CEE or combined HT) relative to the placebo group, which consisted of older women ($P < 0.05$). Effects were small, and decrements were fairly stable. Findings did not vary according to type of HT, prior use or time since last menstrual period ([Espeland 2016](#)).

Gallbladder disease

Researchers have noted a statistically significant association between HT and gallbladder disease, with excess risk related to both oestrogen-only and combined continuous HT. Although most of the statistical power for this outcome was derived from [WHi 1998](#), findings with respect to combined continuous HT were strongly supported by data from both blinded and unblinded follow-up in [HERS 1998](#). [WHi 1998](#) investigators noted that the risk started to increase in the active group during the first year and appeared to increase over time. They calculated that for one excess case of gallbladder disease, 323 women would need to take oestrogen-only HT, or 500 women would need to take combined continuous HT for a year.

Overall completeness and applicability of evidence

Type of HT

Nearly all statistically significant findings described in this review derived from the two biggest studies - [HERS 1998](#) and [WHi 1998](#). Both studies evaluated oral conjugated equine oestrogen (CEE) 0.625 mg, with or without continuous methoxyprogesterone (MPA 2.5 mg). Smaller studies using other types of HT reported very few or no major clinical events. We were generally unable to combine results from individual studies because they used different types of HT, which may not be equivalent in effect, or they differed with respect to the study population, or both. Controversy surrounds the degree to which the findings of [WHi 1998](#) apply to any type of HT other than continuous combined oral CEE 0.625 mg with or without MPA 2.5 mg. Effects may vary with different oestrogens and progestogens, different time frames for the use of HRT and different doses and routes of administration (e.g. unopposed oestrogen and intrauterine progestogen). Observational evidence shows that transdermal oestrogen differs from oral oestrogen in that it is not associated with increased risk of venous thromboembolism and suggests that some types of progestogen are thrombogenic but others are safe in this respect ([Canonico 2007](#)).

Population characteristics

It is important to consider any increased risk to health in absolute rather than relative terms. This review is inevitably dominated by the findings of [WHi 1998](#), which was designed to evaluate the efficacy of HT in preventing major causes of morbidity and mortality among older women ([Matthews 1997](#)). It was not designed to evaluate the risks and benefits of hormone therapy for treatment of menopausal symptoms, and it specifically excluded women who reported menopausal symptoms severe enough to preclude assignment to placebo treatment ([Anderson 2003](#)). Moreover, [WHi 1998](#) did not include women younger than 50 years of age, and study findings may not apply to young surgically menopausal women, for example, a woman who has had both ovaries removed while in her forties ([Kaunitz 2002](#)).

Evidence is lacking on the long-term effects of HT on healthy younger women, who are most likely to use it for menopausal symptoms. Such women are likely to be in their early fifties, when the absolute risk of a life-threatening event is low; it has been estimated that absolute risk for many diseases approximately doubles with each decade of age ([Hulley 2004](#)). Subgroup analyses of women 50 to 59 years of age in [WHi 1998](#) (combined HT arm) revealed that for relatively healthy women taking combined continuous HT, the only increase in risk that reached statistical significance was risk of venous thrombosis. Risk in the HT group increased from eight venous thromboses per 10,000 women per year to 19 per 10,000 women per year. This increase in risk was highest during the first year of therapy but continued over 5 years of treatment, and it was particularly high in obese women (i.e. women with a body mass index greater than 30), who had a 5-year risk of 1.4% compared with 0.5% among women of normal weight. In the oestrogen-only arm of [WHi 1998](#), over the full 10.7 years of intervention and extended follow-up, younger women (aged 50 to 59 years) randomised to HT had significantly more favourable outcomes than those randomised to placebo. The HT group had significantly lower hazard ratios for coronary heart disease, myocardial infarction and death when compared with the placebo group. Findings were similar for both coronary outcomes when data were stratified by time since menopause rather than by age. This contrasted with findings in older women, among whom those in the HT group showed a trend for higher rates of coronary heart disease, myocardial infarction and death, and significantly higher rates of colorectal cancer and chronic disease. [WHi 1998](#) authors noted that study participants took unopposed oestrogen for a median duration of less than 6 years, and that study results cannot be extrapolated to longer or shorter treatment durations. Moreover, it is important to note that oestrogen-only HT is contraindicated for women with an intact uterus, as use from 1 to 5 years has been estimated to increase the risk of endometrial cancer threefold (from a baseline lifetime risk of about 3% for a woman of 50), with effects persisting for several years after oestrogen is stopped ([Grady 1995](#)).

It has been suggested that effects of HT may differ according to whether it is initiated soon after menopause or after a lengthy gap ([Barret-Connor 2007](#)). Analysis of randomised ([Prentice 2009a](#)) and observational ([WHi 1998](#)) data revealed that for most clinical outcomes, effects of HT did not vary by HT timing; this applied to both oestrogen-only and combined HT. One exception was breast cancer, for which risk was higher among women who initiated HT soon after menopause than in those who had a longer time gap. Their overall risk of cancer was also higher.

HT appears to carry increased risk of recurrence for women with a history of breast cancer. Two unblinded studies conducted in Sweden randomised breast cancer survivors with menopausal symptoms to HT or non-hormonal treatment. Both studies were terminated early owing to a statistically significant increase in the incidence of recurrent breast cancer in the hormonal group in one of the studies (risk ratio (RR) 3.5, 95% confidence interval (CI) 1.5 to 8.1) ([Chlebowski 2004](#); [Holmberg 2004](#)). After a median of 4 years' follow-up in this study, a clinically and statistically significantly increased risk of a new breast cancer event continued in the HT arm (RR 2.4, 95% CI 1.3 to 4.2) ([Holmberg 2008](#)). A similar study initiated in the UK terminated recruitment prematurely in January 2004 ([ICR 2001](#)).

For cardiovascular outcomes, results of [HERS 1998](#) largely support the results of [WHI 1998](#) (combined HT arm), suggesting that these findings can be generalised to older women taking combined continuous HT, whether or not they have known cardiovascular risk factors (although their findings differ with respect to fracture risk).

Health benefits and risks after stopping HT

[WHI 1998](#) (combined HT arm) reported health outcomes at a mean of 2.4 years' extended follow-up after the planned intervention period ([Heiss 2008](#)). Follow-up data for this period were available for 95% of women, few of whom were using HT during extended follow-up (4.3% in the intervention arm and 1.2% in the placebo arm at 1 year after the study was stopped). Over the course of follow-up, risk of coronary events, stroke and venous thromboembolism decreased in the group that had been randomised to combined HT, and reached a level comparable with that of the placebo group. Similarly, results showed no significant differences between groups in risk of fractures or of colorectal cancer by the end of postintervention follow-up. However, in the group that had been randomised to combined HT, the hazard ratio (HR) for the outcome "all cancer" increased from 1.03 (95% CI 0.92 to 1.15) during the intervention phase to 1.24 (95% CI 1.04 to 1.48) in the postintervention period. This increase in risk was attributable in part to the disappearance of previous apparent protection from colorectal cancer, with some continued excess risk of breast cancer, along with added risk of lung cancer in the HT group. Study authors noted that clinical vigilance appears to be warranted with regard to sustained higher risk of malignancy following termination of combined HT therapy.

[WHI 1998](#) (oestrogen-only arm) reported health outcomes at a mean of 3.9 years' extended follow-up ([LaCroix 2011](#)). Follow-up data for this period were available for 78% of women, of whom only a small minority were using hormone therapy (up to 4.7% in the intervention arm and 3% in the placebo arm). Over the course of extended follow-up, results continued to show no significant difference between groups in rates of coronary events. Increases in risk of stroke and venous thromboembolism in the HT arm rapidly disappeared, as did reduced risk of hip fracture in this group. As noted above, the lower incidence of breast cancer persisted and became statistically significant with extended follow-up to 10.7 years (i.e. including both planned intervention and extended follow-up periods).

Quality of the evidence

Most of the included studies were at low risk of bias in most domains ([Figure 1](#)). We rated the overall quality of evidence as moderate, and the main limitation involved questions about applicability of the evidence because most of the data were provided by [WHI 1998](#), in which only about 33% of the study sample was 50 to 59 years of age at baseline (i.e. the age at which women are most likely to consider HT for vasomotor symptoms); mean participant age was 63 years.

A high proportion of women in these studies did not receive the treatment to which they were randomised. In general, the number of women who discontinued their medication or who took less than 80% of their medication was disproportionately high in the HT groups, presumably because of a higher incidence of adverse effects such as vaginal bleeding. [WHI 1998](#) noted that if discontinuation of treatment and initiation of non-study treatment

occurred independently of risk factors for clinical outcomes, their intention-to-treat analysis underestimates both harms and benefits of HT among women who adhere to treatment ([WHI 2002](#)). This study included a disproportionate number of women who were unblinded in the HT group compared with the placebo group (40% vs 6%), primarily to manage persistent vaginal bleeding, and it has been suggested that this differential unblinding may have resulted in higher detection rates of otherwise undetectable myocardial infarction in the HT group ([Shapiro 2003](#)). However, it has been suggested that detection bias on a scale that would explain the differences between groups for coronary heart disease could not have occurred, and that any bias was more likely to have occurred in the opposite direction, mitigating against detection of effects ([Tucker 2003](#)).

Potential biases in the review process

This review is subject to patient selection bias. Most of the included studies had a mean participant age over 60 years, and none focused on perimenopausal women. In all but one of the 20 studies that reported mean participant age, mean age at enrolment was over 50 years. This does not reflect usual clinical practice with respect to prescribing of HT, which is most likely to occur for treatment of vasomotor symptoms at the time women reach menopause ([Pedersen 2003](#)). Moreover, participants described as 'relatively healthy' in this review were derived largely from [WHI 1998](#). Investigators reported a high frequency of obesity and hypertensive disorders among [WHI 1998](#) participants; only 30% were of normal weight, and 30% were morbidly obese (body mass index (BMI) > 30 kg/m²); 36% were receiving treatment for hypertension or had blood pressure exceeding 140/90 mmHg at enrolment.

Despite extensive searching, we may have failed to identify all relevant studies. However, it is unlikely that we missed any study large enough to substantially influence our overall findings, given dominance of the review by [WHI 1998](#). Similarly, although our data could conceivably have been organised in a different way (e.g. for categorising of study populations and HT doses), again the dominance of [WHI 1998](#) makes it extremely unlikely that this would have influenced our findings. We chose not to pool studies that used different types of HT, and this approach is supported by contrasting findings in the two arms (combined vs oestrogen-only HT) of [WHI 1998](#) for some outcomes.

The choice of 1 year's duration of HT as a cut-off point for inclusion of studies was arbitrary but is unlikely to have introduced bias, as it was a prespecified criterion.

Agreements and disagreements with other studies or reviews

Our findings are consistent with those of a Cochrane review of HT for preventing cardiovascular disease in postmenopausal women ([Boardman 2015](#)), which concluded that use of HT in postmenopausal women has little if any benefit for primary or secondary prevention of cardiovascular disease and causes an increase in the risk of stroke and venous thromboembolic events. [Boardman 2015](#) differed from the current review in that review authors pooled data related to unopposed oestrogen with data for combined HT.

However, our findings differ from those of some older systematic reviews.

A systematic review of available randomised evidence was conducted in 1997 and was updated with unpublished evidence in 2000 ([Hemminki 1997](#); [Hemminki 2000](#)). Review authors reported a conservatively estimated odds ratio for cardiovascular events of 1.34 (95% CI 0.55 to 3.30) among those taking HT. However, this result was based on only 15 secondary events in those allocated to HT and seven among the control groups and provided insufficient evidence to exclude potential benefit from HT.

[Beral 2002](#) pooled the results of four randomised controlled trials of HT published between 1998 and 2002 ([EVETET 2000](#); [HERS 1998](#); [WEST 2001](#); [WHI 1998](#)). They reported no significant excess or reduction in the risk ratio of CHD, and their findings negated the large beneficial effect of HT reported for cardiovascular outcomes in earlier observational studies. Moreover, they described excess risk of stroke, pulmonary embolus and breast cancer. Review authors found that risk of colorectal cancer or fractured neck of femur was significantly reduced for the HT group, and the findings for endometrial cancer risk were inconclusive. The authors of this review pooled the results of studies that used different types of HT over variable time frames. The most notable difference between the current review and [Beral 2002](#) is that the current review found a statistically significant increase in risk of coronary heart disease among women taking combined continuous HT, particularly in the first year. Unlike the current review, [Beral 2002](#) pooled results from studies of differing participant groups and types of HT; this appears to explain why overall findings differ.

[Salpeter 2004](#) meta-analysed 17 RCTs of HT that reported at least 1 death and concluded that risk of death was significantly reduced in women with a mean age under 60 years who were taking HT compared with those taking a placebo, although results showed no difference when older women were compared. This meta-analysis pooled studies that differed widely with respect to the type of HT used and the clinical status of participants; in several studies, death was not a prespecified outcome. Moreover, women with poor prognosis for ovarian cancer accounted for 60% of events in the meta-analysis of studies of younger women. In the current review, evidence shows no survival advantage for women taking HT, although only one of the included studies ([WHI 1998](#) (oestrogen-only HT)) analysed younger women as a subgroup for this outcome. Of the 17 studies that Salpeter et al included in their meta-analysis of younger women, only two met the inclusion criteria for the present review; the other 15 studies included in the earlier review were not blinded, did not report mortality as a primary or secondary outcome or were of less than 1 year's duration.

A systematic review of studies of hormone therapy and ovarian cancer ([Greiser 2006](#)) included 30 case-control studies, seven cohort studies, one randomised controlled study and four cancer registry studies. This review found increased risk of ovarian cancer associated with the use of oestrogen-only HT (RR 1.28, 95% CI 1.18 to 1.40) or combined hormone therapy (RR 1.11, 95% CI 1.02 to 1.21). This risk applied to a range of common histological subtypes of ovarian cancer. Review authors noted that this review was limited by reliance on observational data; however, heterogeneity was low or moderate in most analyses.

Another systematic review ([Bath 2005](#)) meta-analysed 28 RCTs of HT that reported stroke events. HT was associated with a statistically significant excess risk of stroke, particularly ischaemic stroke. Moreover, participants in the HT group who had a stroke seemed to have a worse outcome. This review had very broad

inclusion criteria and pooled a wide range of studies, which used different types of HT for a range of indications, some with male participants and some without placebo control. It is unclear to what extent these findings apply to perimenopausal and postmenopausal women.

A Danish study ([Schierbeck 2012](#)) of 1006 recently postmenopausal or perimenopausal women (aged 45 to 58 years) was not eligible for this review owing to lack of blinding. Investigators reported that after 10 years of treatment, women taking triphasic 17-B oestradiol with norethisterone acetate or (in those who had had a hysterectomy) oestradiol alone were at lower risk of experiencing their primary outcome - a composite of death and admission to hospital for heart failure or myocardial infarction (hazard ratio 0.48, 95% CI 0.26 to 0.87; $P = 0.015$). No increase in risk of cancer, venous thromboembolism or stroke was apparent. Study authors attributed the difference between their findings and those of [WHI 1998](#) to the younger age and proximity to menopause of their participants. This study was limited by lack of blinding and by the use of a composite primary outcome that was not prespecified in the study protocol ([Marjoribanks 2012](#); [Schroll 2012](#); [Shapiro 2003](#)). It has been noted that the cardiovascular outcomes were not ascertained by researchers but were based on data from individual clinicians entered into a national database ([Abelin 2012](#)).

We found no randomised studies or systematic reviews that provided evidence about the risks of long-term HT in perimenopausal women or those younger than 50 years of age.

Current recommendations favour the use of low-dose HT for relief of vasomotor symptoms among women within 10 years of their last period, taken for the shortest possible time required to achieve treatment goals, with doses individually tailored and reviewed regularly ([NAMS 2012](#); [NICE 2015](#); [RANZCOG 2012](#)).

AUTHORS' CONCLUSIONS

Implications for practice

HT for women with menopausal symptoms

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (e.g. obesity, history of venous thrombosis) or increased risk of some types of cancer (e.g. breast cancer in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented.

Although none of the studies included in this review focused specifically on women in the age group most likely to require menopausal symptom relief, subgroup analyses in [WHI 1998](#) suggested that among relatively healthy women in their 50s taking oestrogen-only or combined HT, the only significant risk was increased incidence of venous thromboembolism in those taking combined HT. Absolute risk of venous thromboembolism was low, at 0.5% overall for a woman taking HT for 5 years. For women in their 50s without a uterus, taking oestrogen-only HT for 5 to 6 years appears relatively safe and may even confer some health benefits. However, safety over longer-term use is unknown.

HT for other indications

HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women.

Although HT is considered effective for prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. Strong evidence suggests that both oestrogen-only HT and combined therapy significantly increase the risk of stroke and gallbladder disease, and that long-term use of combined continuous therapy also increases the risk of coronary events, breast cancer, death from lung cancer and (in women over 65 years of age) dementia.

HT for women with previous disease or smoking history

HT is not recommended for use in women with cardiovascular disease or with a history of venous thrombosis or breast cancer. Randomised evidence provides no specific contraindications for its use in women with a history of endometrial cancer or ovarian cancer, although data are scanty. Women at high risk of lung cancer (current smokers or long-term past smokers) should be aware that combined HT increases the risk of death from lung cancer.

Implications for research

No studies have adequately assessed the safety of HT used for symptom relief by perimenopausal women, women younger than

50 years or women with temporary or permanent iatrogenic ovarian failure. Not enough is known about factors that may modulate the risks involved, such as clinical characteristics or biomarkers affecting individual women, different oestrogens and progestogens, different time frames for the use of HT and different doses and routes of administration (e.g. unopposed oestrogen and intrauterine progestogen, whether the risk of thromboembolism is diminished by the use of patches). Reliable evidence is needed to show the efficacy and safety of alternatives to HT for control of menopausal symptoms among women who may wish to avoid using HT, or for whom its use is unsuitable.

ACKNOWLEDGEMENTS

Thanks to Marian Showell (CFG Information Specialist) who designed and ran the search strategy for the 2012 and 2017 updates of this review, and Josie Rishworth, who helped format the labelling of the analysis tables for the 2012 update. Thanks also to Quirine Lamberts, Jane Suckling and the following Cochrane Review Groups, all of whom helped with the first version of this review: Breast Group, Colorectal Cancer Group, Dementia and Cognitive Improvement Group, Gynaecological Cancer Group, Heart Group, Gynaecology and Fertility Group, Musculoskeletal Group, Peripheral Vascular Diseases Group and Stroke Group. See [Contributions of authors](#) for details. Martha Hickey kindly provided comments and suggestions on drafts of the 2008 update.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Barakat 2006

Methods	<p>Stated purpose: to determine the effect of oestrogen therapy on recurrence rate and survival in women who have undergone surgery for stage I or II endometrial cancer</p> <p>Stratification: stratified by stage</p> <p>No. of women screened for eligibility: unclear</p> <p>No. randomised: 1236 (see Notes)</p> <p>No. analysed: 1236</p> <p>Losses to follow-up: none stated</p> <p>Adherence to treatment: 41% in HT group, 50% in placebo group at trial end</p> <p>Analysis by intention to treat: yes</p> <p>No. of centres: not stated</p> <p>Years of recruitment: June 1997 to January 2003</p> <p>Design: parallel</p> <p>Funding: National Cancer Institute grant</p>
Participants	<p>Included</p> <p>Women post total hysterectomy and bilateral salpingo-oophorectomy (at least) for surgically staged stage I or II endometrial cancer within 20 weeks of study entry, with indication for use of oestrogen therapy including hot flushes, vaginal atrophy, increased risk of CHD or increased risk of osteoporosis. Had to have undergone clinical exam with history, pelvic exam and chest X-ray before study entry. Normal hepatic function and normal mammogram or negative breast biopsy within previous year</p> <p>Excluded</p> <p>Women with history or suspicion of breast cancer or other malignancy with exception of non-melanoma skin cancer within past 5 years or with history of acute liver disease or thromboembolic disease</p> <p>Median age: 57</p> <p>Age range: 26-91</p> <p>Means of recruitment: not stated</p> <p>Baseline equality of treatment groups: well balanced</p> <p>Country: USA</p>
Interventions	<p>HT arm: 0.625 mg CEE (unopposed oestrogen)</p> <p>Control arm: placebo</p>

Barakat 2006 (Continued)

Duration: planned for 3 years with 2 years' additional follow-up. Closed early with median follow-up 35.7 months

Outcomes	Total deaths CHD deaths Coronary event deaths Endometrial cancer deaths Endometrial cancer (recurrence)
Notes	Enrolment decreased after WHI was published in July 2002. Study closed prematurely owing to poor accrual. In addition, preponderance of participants had low risk profile, so low event rate meant power unlikely to be reached with original power calculation. This study planned to enrol 2108 women. Numbers randomised not entirely clear: Study refers to 1236 "eligible and assessable women".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remotely generated
Allocation concealment (selection bias)	Low risk	Remotely dispensed drugs
Incomplete outcome data (attrition bias) All outcomes	High risk	No losses to follow-up reported, but numbers randomised not entirely clear: Study refers to 1236 "eligible and assessable women".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and physicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Review authors believe risk of bias low owing to 'hard' nature of outcomes
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

ELITE 2014

Methods	2 × 2 double-blinded placebo-controlled parallel-group RCT Stated purpose: to assess the effect of HT on progression of subclinical atherosclerosis and cognitive effects initiated between early and late postmenopause Stratification: not stated No. of women screened for eligibility: 3061 (n = 2166 via telephone, n = 895 in person) No. of women randomised: 643 (323 to HT, 320 to placebo; subgrouped by time since menopause with respect to initiation of HT)
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ELITE 2014 (Continued)

No. of women analysed: 567 underwent cognitive baseline assessment, total of 567 women provided cognitive outcomes at 2.5 years and 455 women provided outcomes at 5 years.

Losses to f/u: 2.2% of women were lost to follow-up, and another 10.0% discontinued participation before cognitive outcomes were assessed (14 lost to follow-up, 22 dropouts due to adverse events, 40 discontinued for other reasons before contributing to cognitive outcomes at 2.5 years).

Adherence to treatment: Mean adherence for oestradiol or placebo was $\geq 98\%$ for early and late group women.

Analysis by intention to treat: yes

No. of centres: 1

Years of recruitment: July 2005 and September 2008

Design: parallel

Funding: supported by National Institutes of Health grant for initial and supplemental funding of ELITE and ELITE-Cog. Study drugs and placebo were supplied without charge or restriction by Teva Pharmaceuticals, Watson Pharmaceuticals and Abbott Laboratories.

Participants	643 healthy postmenopausal women with clinical evidence of CVD or diabetes, subgrouped by time since menopause (< 6 years since menopause ($n = 271$) or > 10 years since menopause ($n = 372$))
Included	Women with a serum oestradiol level < 25 picogram/mL and cessation of regular menses > 6 months who are < 6 years and > 10 years postmenopausal
Excluded	Clinical signs, symptoms or personal history of cardiovascular disease, indeterminate time since menopause, DM or fasting serum glucose ≥ 140 mg/dL, uncontrolled hypertension (diastolic blood pressure ≥ 110 mmHg), untreated thyroid disease, serum creatinine > 2.0 mg/dL, plasma triglyceride levels > 500 mg/dL, life-threatening disease with prognosis < 5 years, cirrhosis or liver disease, hx of deep vein thrombosis or pulmonary embolism, history of breast cancer, current HT
Median age:	53.4 years for early, 63.6 years for late
Age range:	41-84
Means of recruitment:	telephone and in person
Baseline equality of treatment group:	no statistically significant difference in baseline characteristics. Women not contributing to analysis were similar to other women in most but not all comparisons.
Country:	USA
Interventions	<ol style="list-style-type: none"> 1. Oral 17β-oestradiol 1 mg daily with (uterine intact) or without (hysterectomy) vaginal micronised progesterone gel 4% (45 mg) 10 days per month: Study publication does not state how many women were in each group. 2. Placebo <p>Originally planned for 5 years, extended to 7.5 years</p>
Outcomes	<p>Primary study outcome</p> <p>Progression of subclinical atherosclerosis - not relevant for current review</p> <p>Secondary outcomes</p>

ELITE 2014 (Continued)

Cognitive function at 2.5 and 5 years, cardiovascular events (fatal or nonfatal MI, silent MI, sudden death), stroke, venous thromboembolism (DVT or PE), cancer (breast, uterine, ovarian, gastrointestinal, lung), bone fracture, all-cause mortality, non-coronary mortality

Notes
 Power calculation: 506 sample size provides power of 80% needed to detect difference in rate of change in carotid artery intima media thickness and effect size of 0.22 in early and late groups combined.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated by computer by study statistician
Allocation concealment (selection bias)	Low risk	"Stratified randomization list [was] used to prepare the study products. After determining a participant's eligibility, clinic staff pulled the next study product in sequence from the appropriate stratum, recorded the product identification number, and dispensed the product".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	567/643 women (88%) analysed for cognitive outcomes at 2.5 years, 455/643 (71%) at 5 years
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, participants, clinic staff and data monitors were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not stated whether outcome assessor blinded, but most probably, as study author mentioned trial was extended before blinding was unmasked after receiving supplementary funding
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No other potential source of bias identified

EPAT 2001

Methods
 Stated purpose: to determine the effect of oestrogen-alone HT on progression of subclinical atherosclerosis in healthy postmenopausal women without preexisting cardiovascular disease, as measured by changes in thickness of carotid artery wall
 Stratification: by low-density lipoprotein cholesterol level (threshold < 4.15 mmol/L), previous duration of HT (threshold < 5 years) and diabetes mellitus status
 Blinding: participants, gynaecologists, clinical staff and image analysts. The data monitor and the data analyst were blinded to treatment assignment until analyses were completed.
 No. of women screened for eligibility: 1161 prescreened by phone, 422 screened on site, of whom 52% randomised
 No. randomised: 222
 No. analysed: 222 for clinical outcomes
 Losses to follow-up: 33 women were not evaluable for primary study endpoints, but clinical endpoints were reported for all.
 Adherence to treatment in evaluable women: During the trial, mean pill adherence was 95% in the oestradiol group and 92% in the placebo group ($P = 0.08$).
 Analysis by intention to treat: yes

EPAT 2001 (Continued)

No. of centres: 1
 Years of recruitment: 1994-1998
 Design: parallel
 Funding: National Institute on Aging

Participants	Included Postmenopausal women aged > 45 years, no preexisting cardiovascular disease, low-density lipoprotein levels > 3.37 mmol/L Excluded Women with previous breast or gynaecological cancer, frequent hot flushes, diastolic blood pressure > 110, uncontrolled diabetes or thyroid disease, abnormal bloods, smokers Mean age: 61.15 Age range: 51.4-69.2 Means of recruitment: not stated Baseline equality of treatment groups: no significant differences in demographics or clinical variables Country: USA	
Interventions	HT arm: unopposed micronised 17B-oestradiol 1 mg daily Control arm: placebo Duration: 2 years	
Outcomes	Primary outcomes Carotid artery wall thickness on ultrasound Myocardial infarction Cerebrovascular accident Transient ischaemic attack Deep vein thrombosis Pulmonary embolism	
Notes	Power calculation: sample size of 200 required to detect treatment effect size (difference in carotid artery wall thickness) of 0.40 or greater with 80% power	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Blinded medication packets assigned sequentially and remotely after eligibility confirmed
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 women were not able to be evaluated for primary (physiological) study endpoints, but clinical endpoints were reported for all by ITT analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, gynaecologists, clinical staff and image analysts. The data monitor and the data analyst were blinded to treatment assignment until analyses were completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Adverse clinical symptoms and bleeding were assessed by the study gynaecologist, who was blinded to treatment assignment".

EPAT 2001 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

EPHT 2006

Methods	<p>Stated purpose: to ascertain harms and benefits of combined HT among healthy postmenopausal Estonian women</p> <p>Stratification: by centre</p> <p>No. of women screened for eligibility: 39,713 (whole female population aged 50-64 from 2 areas of Estonia)</p> <p>No. randomised and consented: 777 for clinical outcomes (Veerus 2006 publication), 796 for quality of life (Veerus 2008 publication) (see Notes)</p> <p>No. analysed: 777 for clinical outcomes (HT 404, placebo 373), 796 for quality of life (HT 415, placebo 381)</p> <p>Losses to follow-up: none stated</p> <p>Adherence to treatment: < 40% in HT group and < 30% in placebo group by 3 years (estimated from graph)</p> <p>Analysis by intention to treat: yes</p> <p>No. of centres: 3</p> <p>Years of recruitment: 1999-2001</p> <p>Design: parallel</p> <p>Funding: academic and government grants</p> <p>www.controlled-trials.com/ ISRCTN35338757/35338757</p>
Participants	<p>Included</p> <p>Postmenopausal women > 12 months since last period</p> <p>Excluded</p> <p>Women who had used hormone therapy during the past 6 months; with untreated endometrial adenomatosis or atypical hyperplasia of the endometrium; history of breast cancer, endometrial cancer or ovarian cancer; any other cancer treated less than 5 years ago; history of meningioma; myocardial infarction within the past 6 months; history of hepatitis or functional liver disorders in the past 3 months; history of deep vein thrombosis, pulmonary embolism or cerebral infarction; porphyria; hypertension greater than 170/110 mmHg despite medication; laparoscopically or histologically confirmed endometriosis</p> <p>Mean age: 59</p> <p>Age range: 50-70</p> <p>Means of recruitment: invitation sent to whole female population aged 50-64 from 2 areas of Estonia</p> <p>Baseline equality of treatment groups: more prior use of oral contraceptive in HT group - 9.2% vs 6.4%; HT group older (59 vs 58.5)</p> <p>Country: Estonia</p>
Interventions	<p>HT arm: combined oestrogen and progesterone as 1 daily tablet containing CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg</p> <p>Control arm: matching placebo</p> <p>Duration: mean follow up 3.43 years (range 2-5). Planned for 10-year follow-up but closed early</p>
Outcomes	<p>Death</p> <p>CHD</p> <p>Cancers</p> <p>Fractures</p> <p>CVD</p>

EPHT 2006 (Continued)

Quality of life measured with EuroQol-5D questionnaire at 3 years (also measured with Women's Health Questionnaire at 1 year), but no baseline measure, and results pooled for blinded and unblinded HT arms (data not reported in this review)

Notes	Women randomised before eligibility and consent checked - envelopes opened only once these processes were completed. Additional 1001 women in unblinded trial arms Designed as part of international WISDOM trial Mean follow-up only 3.43 years (range 2-5) for clinical outcomes, 3.6 years for quality of life. Planned for 10-year follow-up but closed early
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remotely randomised in permuted blocks
Allocation concealment (selection bias)	Low risk	Non-transparent sealed envelopes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No stated losses to follow-up or drop-outs, analysed by intention to treat. However, stated participation rates differ slightly across trial publications (796 vs 777).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessed by entries in cancer registry - review authors believe low risk of bias
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Quality of life not measured (with EuroQol-5D) at baseline - possible baseline differences

ERA 2000

Methods	Stated purpose: to evaluate effects of HT on progression of coronary atherosclerosis Stratification: according to lipid lowering therapy at baseline and hospital where angiogram was performed Blinding: participants, clinic staff and all outcome assessors blinded Unblinding: treatment assignment available to designated member of data management staff. Questions related to adverse effects directed to gynaecology physician and nurse not connected with study No. of women screened for eligibility: not stated No. randomised: 309 No. analysed: 309 (for clinical events) Losses to follow-up: none (for clinical events) Adherence to treatment in 248 participants evaluated was as follows: Unopposed oestrogen group took 74.5% of their prescribed medication, and combined HT group took 84%; placebo group took 85.8%. 5 women in the placebo group started to take HT.
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ERA 2000 (Continued)

Analysis by intention to treat: Although only 248 participants were available for the primary trial endpoint (which was biological), clinical adverse events, including outcomes of interest to this review, were reported for all participants at 3.2 years by intention to treat.

No. of centres: 6

Years of recruitment: January 1996–December 1997

Design: parallel

Funding: grants from National Heart, Lung and Blood Institute and National Center for Research Resources General Clinical Research Center, study medications from Wyeth-Ayerst Research

Participants	<p>Included</p> <p>Postmenopausal women aged 55–80 years (non-natural menses for at least 5 years, or for 1 year and FSH > 40 mu/mL or oophorectomy) with at least 1 stenosis > 30% in any single coronary artery confirmed by coronary angiography within 4 months of randomisation, baseline gynaecological examination normal</p> <p>Excluded</p> <p>Failure to achieve > 80% compliance during 4-week placebo run-in phase, breast or endometrial cancer, history of DVT or PE, symptomatic gallstones or elevated liver enzymes, fasting plasma triglycerides > 400 mg/dL, MI within 4 weeks, renal insufficiency, dye allergy, > 70% stenosis of coronary artery, uncontrolled hypertension, uncontrolled diabetes, planned or prior coronary artery bypass graft, revascularisation of only qualifying lesion (for study), inadequate baseline angiogram for study, other non-CHD disease likely to be fatal or to prevent adequate follow-up, participation in other intervention studies, plans to leave area within 3 years</p> <p>Mean age: 66</p> <p>Age range: 41.8–79.9</p> <p>Means of recruitment: media announcements, contact through hospital records and admissions, screening logs from other studies</p> <p>Baseline equality of treatment groups</p> <p>Country: USA</p> <p>Follow-up: 3 months, 6 months, then 6-monthly clinic visits; annual smear and mammography, annual endometrial aspiration</p>	
Interventions	<p>HT arm: 1 of the following</p> <ol style="list-style-type: none"> 1. 0.625 mg CEE (unopposed oestrogen) 2. 0.625 mg CEE plus 2.5 mg MPA (combined continuous therapy) <p>Control arm: placebo</p> <p>Duration: 3.2 years mean</p>	
Outcomes	<p>Primary outcome angiographic</p> <p>MI</p> <p>Stroke</p> <p>Death</p> <p>DVT</p> <p>PE</p>	
Notes	Power calculation: 80% power for primary angiographic outcome	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised in random blocks
Allocation concealment (selection bias)	Low risk	Computer-displayed treatment assignment after eligible participant details entered
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up for clinical adverse events. Analysed by intention to treat

ERA 2000 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	More in unopposed oestrogen group using nitrates at baseline; otherwise prognostic balance between groups

ESPRIT 2002

Methods	<p>Stated purpose: to ascertain whether unopposed oestrogen reduces the risk of further cardiac events in postmenopausal women who survive a first myocardial infarction</p> <p>Stratification: by clinical centre</p> <p>Blinding: participants, clinicians, outcome assessors. Pharmaceutical company dispensed medication/placebo in identical numbered packages.</p> <p>Unblinding: on request of family doctor or if participant withdrew from treatment (in later stages of study, only if withdrawing participant had not had a hysterectomy). Outcome assessors remained blinded throughout.</p> <p>No. of women screened for eligibility: 3121 met inclusion criteria for MI (reasons for non-participation listed in study).</p> <p>No. randomised: 1017</p> <p>No. analysed: 1017</p> <p>Drop-outs: Drop-outs included 43 women in the HT group (8%) and 57 in the placebo group (11%) who did not take any of the trial medication.</p> <p>Losses to follow-up: none</p> <p>Known non-adherence with allocated treatment was as follows: At 1 year, 51% of participants on the HT arm and 31% on the placebo arm were not taking their allocated tablets regularly. At 2 years, 57% of participants on the HT arm and 37% on the placebo arm were not taking their allocated tablets regularly.</p> <p>Analysis by intention to treat: yes</p> <p>No. of centres: 35</p> <p>Years of recruitment: July 1996-Feb 2000</p> <p>Design: parallel</p> <p>Funding: Schering AG provided medication.</p>
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Participants
Included

Postmenopausal women admitted to coronary care units or general medical wards at participating centres, who met diagnostic criteria for myocardial infarction, were discharged alive within 31 days of admission

Excluded

Women with previously documented MI who had used HT or had vaginal bleeding in the 12 months before admission, history of breast, ovarian or endometrial cancer, active thrombophlebitis, history of DVT or PE, liver disease, Rotor syndrome, Dubin-Johnson syndrome or severe renal disease

Mean age: 62 years (SD 5)

Means of recruitment: Research nurses checked hospital case notes and approached potentially eligible women if their family doctor agreed to collaborate.

ESPRIT 2002 (Continued)

	Baseline equality of treatment groups: yes Countries: England and Wales
Interventions	HT arm: unopposed oestradiol valerate 2 mg daily Control arm: placebo Duration: 2 years
Outcomes	Recurrent MI Cardiac death All-cause death Endometrial cancer Breast cancer Stroke Thromboembolism
Notes	Power calculation: needed 1700 participants to give 80% power to detect 33.3% decrease in incidence of non-fatal reinfarction or cardiac death (2-sided P = 0.05) Accrual lower than anticipated: Study closed with only 1017 participants, giving 56% power to detect above-mentioned outcomes, assuming full compliance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers generated by trial statistician in blocks of 4
Allocation concealment (selection bias)	Low risk	Women assigned consecutively to numbers kept on list accessible to statistician only
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up; analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

EVTET 2000

Methods	Stated purpose: to determine if HT alters risk of venous thromboembolism in high-risk women Randomisation method: computer-generated 1:1 block randomisation with fixed block sizes of 10 Allocation method: not described Stratification: by age < 60 years or ≥ 60 years; 37 (23 HT and 14 placebo) women did not attend all visits owing to premature termination of the study Blinding: double-blind No. of women screened for eligibility: 328
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EVTET 2000 (Continued)

No. randomised: 140 (71 HT, 69 placebo)
 No. analysed: 140
 Losses to follow-up: nil, although 37 (23 HT and 14 placebo) women did not attend all visits owing to premature termination of the study
 Adherence to treatment: 33 dropouts: 10 in HT group (2 wanted to be sure of being treated with oestrogen for postmenopausal symptoms, 8 had adverse effects), 23 in the placebo group (11 wanted to be sure of being treated with oestrogen for postmenopausal symptoms, 10 had adverse effects, 2 no reason stated)
 Analysis by intention to treat: Main findings were not reported by intention to treat because dropouts from the placebo group were not included in the denominator for the rate of recurrent thromboembolism. We included all randomised participants in analysis for this review.
 No. of centres: not stated
 Years of recruitment: February 1996–March 1999
 Design: stratified double triangular sequential design
 Funding: Novo-Nordisk Pharmaceutical and research forum Ulleval University Hospital

Participants	<p>Included</p> <p>Postmenopausal women with history of VTE, aged < 70 years, previous VTE verified by objective means (i.e. venography or ultrasonography in cases of DVT; lung scan, helical computed tomography or angiography in cases of PE)</p> <p>Excluded</p> <p>Current use or use of anticoagulants within past 3 months, familial antithrombin deficiency, any type of malignant disease including known, suspected or past history of carcinoma of the breast; acute or chronic liver disease or history of liver disease in which liver function tests had failed to return to normal; porphyria; known drug abuse or alcoholism; life expectancy less than 2 years; women who had taken part in other clinical trials within 12 weeks before study entry</p> <p>Mean age: 55.8 years Age range: 42–69 years Means of recruitment: letters to family doctors, gynaecologists and hospitals, health bulletins and media Baseline equality of treatment groups: Baseline characteristics were similar for HT group and placebo group with regard to previous disease (coronary heart disease, hypertension, stroke, diabetes), smoking habits and serum lipids. All women had previously suffered at least 1 VTE, and the total number of previous VTEs was 75 in the placebo group and 77 in the HT group. Country: Norway</p>
Interventions	<p>HT arm: 2 mg oestradiol plus 1 mg norethisterone acetate 1 mg Control arm: placebo Duration: planned 2 years, stopped prematurely at median 1.3 years' follow-up</p>
Outcomes	<p>Venous thrombosis Myocardial infarction Transient ischaemic attacks Stroke</p>
Notes	<p>Study was terminated early; only 140 women enrolled of 240 planned</p> <p>Power calculation: At a significance level of 5% and a power of 90%, sample size was estimated to a maximum of 240 women.</p> <p>After publication of results of the HERS study, which showed as a secondary endpoint increased risk of VTE, recruitment of women was discontinued in September 1998, until reviewed by the safety monitoring committee. The committee was also concerned about a non-significant clustering of endpoints in 1 study group, without knowing treatment allocation. The committee advised on premature termination of the study, even though formal boundaries showing excess risk of VTE were not reached. The final decision on termination of the study was made in February 1999, and by the end of March 1999, all participants had completed a final follow-up visit.</p>

EVTET 2000 (Continued)
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 1:1 block randomisation with fixed block sizes of 10
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Main findings were not reported by intention to treat because drop-outs from the placebo group were not included in the denominator for the rate of recurrent thromboembolism.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel - "equal-looking" placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Selective reporting (reporting bias)	Low risk	Retrospectively registered protocol on trials register. Reports all expected outcomes
Other bias	Low risk	No apparent source of other bias

Ferenczy 2002

Methods	Stated purpose: to assess endometrial safety and bleeding patterns of 17B-oestradiol sequentially combined with dydrogesterone Stratification: not mentioned Blinding: double-blinded No. of women screened for eligibility: 844 No. randomised: 595 (HT group 1: 117, HT group 2: 114, HT group 3: 117, HT group 4: 118, placebo group: 113 (see Interventions)) No. analysed: 442 (for endometrial cancer, which is the only outcome of interest for this review) Losses to follow-up: Endometrial status was evaluated by a biopsy, which was available only for women who remained on active treatment for over a year, or who received placebo and completed the 2-year study. This resulted in 153 losses to follow-up for this outcome (87 from active treatment groups (24%) and 50 from the placebo group (44%), plus another 16 who received no study medication). Adherence to treatment: not reported Analysis by intention to treat: no No. of centres: multi-centre (number not stated) Years of recruitment: not stated Design: parallel Funding: Solvay Pharmaceutical
Participants	<p>Included</p> Postmenopausal women with a uterus with amenorrhoea of at least 6 months or surgically postmenopausal (following bilateral oophorectomy without hysterectomy, more than 3 months before enrolment), FSH within normal postmenopausal range

Ferenczy 2002 (Continued)

Abnormal (uninvestigated bleeding) vaginal bleeding, use of oestrogens and/or progestogens and/or androgens in the preceding 6 months or more, and any previous use of oestradiol pellet/implant therapy
 Age range: 45-65
 Baseline equality of treatment groups: yes
 Countries: Canada and Netherlands

Interventions	HT arm	
	1 mg/d 17B-oestradiol/ 5 mg dydrogesterone for the last 14 days of each 28-day cycle	1 mg/d 17B-oestradiol/10 mg dydrogesterone for the last 14 days of each 28-day cycle
	2 mg/d 17B-oestradiol/10 mg dydrogesterone for the last 14 days of each 28-day cycle	2 mg/d 17B-oestradiol/20 mg dydrogesterone for the last 14 days of each 28-day cycle
	Control arm: placebo	
	Duration: 26 cycles (104 weeks)	
Outcomes	Endometrial cancer	
Notes	Power calculation: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Endometrial status was evaluated by a biopsy, which was available only for women who remained on active treatment for over a year, or who received placebo and completed the 2-year study. This resulted in 153 losses to follow-up (26%) for this outcome.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blinded - review authors believe risk of bias low owing to 'hard' nature of outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Review authors believe risk of bias low owing to 'hard' nature of outcomes
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

Greenspan 2005

Methods	Stated purpose: to determine effects of HT on clinical outcomes, including cognitive function, in elderly women Stratification: no Blinding: double-blinded Unblinding: not described No. of women screened for eligibility: 573
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Greenspan 2005 (Continued)

No. randomised: 373 (187 to HT, 186 to placebo)
 No. analysed: 373
 Losses to follow-up: 8 (6 in HT group, 2 in placebo group)
 Adherence to treatment: 61% on HT, 67% on placebo
 Analysis by intention to treat: yes
 No of centres: 1
 Years of recruitment: study conducted January 1996-May 2001
 Design: parallel
 Funding: academic research funding. Pharmaceutical companies provided the drugs.

Participants	<p>Included</p> <p>Community-dwelling women aged 65 years or older with (n = 243) or without (n = 130) a uterus, with complete medical history, physical examination and lab evaluation; tolerated HT in run-in phase</p> <p>Excluded</p> <p>Women with any illnesses or taking medications that could affect bone mineral metabolism within past year, or with known contraindication to HT</p> <p>Mean age: 71 years</p> <p>Age range: 65-90</p> <p>Means of recruitment: advertisements, presentations, physical referrals</p> <p>Baseline equality of treatment groups: yes</p> <p>Country: USA; n = 373 healthy women, mean age 71.3 years, 243 with a uterus and 130 without a uterus</p>
Interventions	<p>Three-month open run-in phase on HT</p> <ol style="list-style-type: none"> 1. CEE oral (0.625 mg/d) or CEE oral (0.625 mg/d) + medroxyprogesterone acetate (2.5 mg/d) in women with a uterus 2. Placebo
Outcomes	MMSE, breast cancer, DVT, clinical fractures, colon cancer (and other outcomes not relevant to this review)
Notes	Half of participants also took alendronate; all took calcium and vitamin D supplement and a multi-vitamin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised lists "prepared by study statistician"
Allocation concealment (selection bias)	Low risk	Research pharmacist assigned treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis; low losses to follow-up (6/373)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Those who assessed the outcomes were blinded to treatment assignment... block sizes randomly determined to enhance blinding of study staff"

Greenspan 2005 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Possibly some potential for confounding from 3-month run-in phase on HT and concurrent use of alendronate

HERS 1998

Methods	Stated purpose: to determine if combined HT alters risk for CHD events in postmenopausal women with established coronary disease
	Stratification: by clinical centre
	Blinding: participants, clinical centre staff, outcome assessors, data analysts, funders blinded
	Unblinding: When required for safety or symptom control, participants reported directly to gynaecology staff, who were located separately from clinical staff, did not communicate with them about breast or gynaecological problems and were not involved in outcome ascertainment.
	No. of women screened for eligibility: 3463, of whom 43% were excluded (ineligible, declined to participate, did not return for appointment or did not comply with placebo run-in therapy)
	No. randomised: 2763
	No. analysed: 2763
	Losses to follow-up: vital status known for all women at end of trial. 59 women did not complete follow-up (32 in experimental arm, 27 in placebo arm).
	Adherence to treatment by women evaluated: by self-report: at 1 year: 82% HT arm, 91% control arm; at 3 years: 75% HT arm, 81% control arm; by pill count in HT arm: at 1 year: 79%; at 3 years: 70% HT arm
	Analysis by intention to treat: yes (also analysed by treatment received, with inclusion limited to women with > 80% compliance)
	No. of centres: 20
	Years of recruitment: February 1993-September 1994
	Design: parallel
	Funding: pharmaceutical (Wyeth-Ayerst)
UNBLINDED CONTINUATION OF HERS 1998:	
	N.B. Follow-up continued unblinded, as an open-label observational study
	2321 women (93% of 2510 surviving HERS participants) followed up for a further 2.7 years - originally planned for additional 4 years, but executive committee decided no further useful information likely to emerge
	No. analysed: 2311 for vital status
	Losses to follow-up: 10 women (1%) not contacted at final follow-up (2 in HT arm, 8 in control arm); of these, vital status known for 5
	Adherence to treatment: Among women originally assigned to the HT group, 45% reported at least 80% compliance during the sixth year of follow-up. Among women originally assigned to placebo, 8% reported taking HT at 6 years.
Participants	Included
	Postmenopausal women younger than 80 years, with a uterus, with coronary disease (myocardial infarction, coronary artery bypass surgery, percutaneous coronary revascularisation or angiographic evidence of at least 50% narrowing of 1 or more major arteries, as documented by baseline ECG or hospital discharge summary), likely to be available for follow-up for at least 4 years
	Excluded
	Women whose coronary event occurred within 6 months of randomisation, use of hormone therapy within 3 months of randomisation, serum triglycerides ≥ 300 mg/dL, history or baseline findings suggestive of venous thromboembolism, breast cancer, endometrial cancer, cervical cancer, uncontrolled hypertension, uncontrolled diabetes, severe congestive heart failure, other life-threatening disease, alcoholism, drug abuse, history of intolerance of HT, any preexisting condition indicating unsuitability for long-term HT or placebo therapy, > 80% compliance with placebo medication during run-in phase
	Mean age: 67 years (SD 7)
	Age range: 44-79

HERS 1998 (Continued)

Means of recruitment: lists of cardiac patients, mass mailing, direct advertising
 Baseline equality of treatment groups: more women in control arm on statins at randomisation (67% vs 54%). When adjusted in analyses - made no statistically significant difference
 Country: USA

Interventions	HT arm: conjugated equine oestrogen 0.625 mg with medroxyprogesterone acetate 2.5 mg Control arm: placebo identical in appearance Continuous oral regimen Adherence to treatment defined as > 80% compliance with medication or placebo Duration: 4.2 years, mean FOR UNBLINDED CONTINUATION OF HERS 1998: Continuation planned for an additional 4 years but stopped after mean additional 2.7 years, as no additional useful data anticipated
Outcomes	Coronary events (MI or coronary death) Venous thromboembolism Fracture Gallbladder disease Endometrial, breast or ovarian cancer Death
Notes	Power calculation: 90% power to observe 24% reduction in coronary events at an average of 4.2 years' ($P = 0.05$) follow-up Further unblinded follow-up 2.7 years (HERS II) - see below

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in blocks of 4
Allocation concealment (selection bias)	Low risk	Computer displayed after participant details entered
Incomplete outcome data (attrition bias) All outcomes	Low risk	Vital status known for all women at end of trial. 59 women did not complete follow-up (32 in experimental arm, 27 in placebo arm). Analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, clinical centre staff, data analysts and funders blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	More women in control arm on statins at randomisation (67% vs 54%). When adjusted in analyses - made no statistically significant difference

KEEPS 2012

Methods	<p>Stated purpose: to test whether menopausal HT initiated within 3 years of menopause can delay progression of atherosclerosis</p> <p>Stratification: by study centre</p> <p>No. of women screened for eligibility: 4532</p> <p>No. randomised: 727 (oral HT: 230, transdermal HT: 222, placebo: 275)</p> <p>No. analysed: 580</p> <p>Losses to follow-up: in oral HT, transdermal HT and placebo groups, respectively, for the following reasons: withdrawals for AEs = 16/230, 9/222, 12/275; personal reasons 11/230, 8/222, 24/275; non-adherence 1/230, 4/222, 3/275; unknown reasons 15/230, 22/222, 18/275</p> <p>Drop-outs/adherence to treatment: 11% of women non-adherent with treatment but included in analysis (116/580)</p> <p>For KEEPS-COG study, sample sizes were oral HT: 220, transdermal HT: 211, placebo: 262.</p> <p>Analysis by intention to treat: no - data not imputed for women lost to follow-up</p> <p>No. of centres: 9</p> <p>Years of recruitment: 2005-2008</p> <p>Design: double-blinded parallel-group RCT</p> <p>Funding: Aurora Foundation (not-for-profit) and other academic grants. Study medications provided in part by pharmaceutical companies</p>
Participants	<p>Included</p> <p>Women aged 42-58 within 6-36 months of final menses</p> <p>Excluded</p> <p>Women post hysterectomy, BMI > 35 kg/m², low-density lipoprotein cholesterol > 160 mg/dL, coronary artery calcium over 50 Agaston units at baseline, smoking over 10 cigarettes per day, history of diabetes, myocardial infarction, stroke, thromboembolic disease or cancer</p> <p>Mean age: 52.7 years, mean 1.8 years since menopause</p> <p>Age range: 42-58</p> <p>Means of recruitment: mass mailings, posters, print and online advertising, Internet web page</p> <p>Baseline equality of treatment groups: high-density lipoprotein cholesterol lower in placebo group, otherwise no statistically significant difference in baseline characteristics</p> <p>Country: USA</p>
Interventions	<p>HT arm</p> <p>0.45 mg/d oral CEE + cyclic oral micronised progesterone 200 mg/d × 12 days per month</p> <p>0.05 mg/d transdermal oestradiol + cyclic oral micronised progesterone 200 mg/d × 12 days per month</p> <p>Control: placebo</p> <p>Duration: 4 years (original protocol was for 5 years, shortened during first year after reconsideration of study design)</p>
Outcomes	<p>Primary outcome: carotid artery intima media thickness</p> <p>Outcomes relevant to this review: quality of life, clinical CVD events (including MI, stroke) reported as adverse events</p> <p>Cognition: KEEPS-COG ancillary study enrolled 93% of women in KEEPS 2012 (participation by invitation). Measured with MMSE</p> <p>Global cognitive function also reported in a subset of participants (CEE 29, combined HT 59, placebo 36) in conjunction with magnetic resonance imaging monitoring of brain structure: data not included in this review (Kantarci 2015)</p>
Notes	

Risk of bias

KEEPS 2012 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomly sequenced blocks of 13 in a ratio 4:4:5 (oral CEE/transdermal CEE/placebo)
Allocation concealment (selection bias)	Low risk	Remotely generated sequence; database key not accessible to study personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	80% of women included in analysis for primary clinical endpoint at 4 years (580/727): 43 withdrew in each HT group, 57 withdrew in placebo group 619/693 (89%) women in KEEPS-COG were included in analysis (85% of total KEEPS sample)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study pharmacist provided blinded packets of study drugs for each participant.
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Outcome assessors blinded to study allocation
Selective reporting (reporting bias)	Low risk	Reports all expected outcomes and all outcomes planned in protocol. Reporting of AEs actively solicited
Other bias	Low risk	No other source of potential bias identified

Mulnard 2000

Methods	Stated purpose: to determine whether oestrogen-only HT affects global, cognitive or functional decline in women with mild to moderate Alzheimer's disease Stratification: not mentioned No. of women screened for eligibility: 153 No. randomised: 120 (CEE 0.625 mg: 42, CEE 1.25 mg: 39, placebo: 39) No. analysed: 120 Losses to follow-up: nil Adherence to treatment: 23 drop-outs (7 in placebo group, 7 in CEE 0.625 mg group, 9 in CEE 1.25 mg/d). Adherence to treatment was measured and was defined as the proportion of individuals who ingested at least 80% of the study medication but was not reported in the trial publication. Analysis by intention to treat: yes No. of centres: 32 Years of recruitment: not stated Design: parallel placebo-controlled Funding: National Institute on Aging, Wyeth Ayerst
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Participants	Included <p>Women with a diagnosis of probable Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association Criteria in mild or moderate stage (study protocol specified MMSE score of 14-28; several exceptions were made by the project director to allow for participants with MMSE scores as low as 12); female sex; previous hysterectomy (oophorectomy not required); older than 60 years; absence of major clinical depressive disorder (as measured by score < 17 on the Hamilton Depression Rating Scale (Ham D); normal gynaecological, breast and mammography results</p> Excluded
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Mulnard 2000 (Continued)

Myocardial infarction within 1 year, history of thromboembolic disease or hypercoagulable state, hypertension, use of excluded medications (i.e. oestrogens within 3 months; current use of antipsychotics, anticonvulsants, anticoagulants, beta-blockers, narcotics, methyldopa, clonidine or prescription cognitive-enhancing or antiparkinson medications, including experimental medications within 60 days before baseline. Stable doses of neuroleptics, antidepressants, anxiolytics, sedatives and hypnotics were allowed). At initiation of the protocol, individuals treated with donepezil or tacrine were excluded, but a protocol amendment after 20 months of enrolment allowed stable use (minimum of 4 weeks) of these medications before screening for the study

Mean age: 75

Age range: 56-91

Means of recruitment: not stated

Baseline equality of treatment groups: no significant differences between the 3 groups in terms of baseline and demographic characteristics

Country: USA

Interventions	HT arm CEE oral 0.625 mg/d CEE 1.25 mg/d Control: placebo Duration: 1 year
Outcomes	Primary outcome Progression of Alzheimer's disease (Alzheimer's Disease Co-operative Study version of the Clinical Global Impression of Change Scale)
Notes	Power calculation: 81% to detect a 29% difference in the proportion of participants who worsened in the 2 groups (60% worse in the placebo group vs 31% worse in the oestrogen group) using a 2-tailed (α) = .05 (based on data from a similar trial, with 40 participants receiving placebo and 80 receiving oestrogen) * Inclusion criteria state > 60 years, but age range at baseline was 56-91

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated in blocks of 6
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up stated. Analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blinded; used "identically appearing tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blinded; no further details
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Inclusion criteria state > 60 years, but age range at baseline 56-91

Nachtigall 1979

Methods	Stated purpose: to evaluate effects of HT Stratification: not mentioned Unblinding: code broken if a major medical complication or death occurred (13 times in HT group, 17 times in control group) No. of women screened for eligibility: 403 (235 excluded: 74 ineligible, 31 refused, 130 no match for pair found) No. randomised: 168 No. analysed: 168 Losses to follow-up: none Adherence to treatment: not mentioned Analysis by intention to treat: yes, although any events occurring after unblinding were not recorded No. of centres: 1 Years of recruitment: unclear - study lasted 10 years and was complete by 1976 Design: parallel Funding: not stated													
Participants	<p>Included</p> <p>Postmenopausal inpatients with chronic disease (last menstrual period > 2 years previously, FSH > 105.5 mU, total urinary oestrogen < 10 micrograms/dl), never taken HT. All hospitalised for entire study period; screened with history, physical examination, medical record review; matched on the basis of chronic disease diagnosis, as follows: diabetes mellitus (14 pairs), custodial care (20 pairs), arteriosclerosis (9 pairs). Other pairs matched on the basis of chronic neurological disorders</p> <p>Excluded</p> <p>Acute heart disease, hypertension (blood pressure > 160/94), apparent malignancy, hysterectomy Mean age: 55 Baseline equality of treatment groups: Correlation for diagnosis was identical. Correlation for some other risk factors was low between individual pairs, but group means were similar. Country: New York Hospital for Chronic Diseases</p>													
Interventions	HT arm: CEE 2.5 mg daily, plus MPA 10 mg for 7 days each month Control arm: placebo Duration: 10 years													
Outcomes	Death, myocardial infarction, "serious embolism" (pulmonary embolus), breast cancer, colon cancer, endometrial cancer, gallstones													
Notes	Power calculation: not mentioned Re generalisability: Study authors point out that almost all women had long-term chronic disease, were hospitalised for the entire study period, had much lower than normal overall parity and had more prolonged bed rest than the average woman.													
Risk of bias														
<table border="1"> <thead> <tr> <th>Bias</th> <th>Authors' judgement</th> <th>Support for judgement</th> </tr> </thead> <tbody> <tr> <td>Random sequence generation (selection bias)</td> <td>Unclear risk</td> <td>Women matched for diagnosis of chronic disease. From matched pairs, research nurse randomly selected which member would be assigned to which group. Method not described</td> </tr> <tr> <td>Allocation concealment (selection bias)</td> <td>Unclear risk</td> <td>Not described</td> </tr> <tr> <td>Incomplete outcome data (attrition bias) All outcomes</td> <td>Low risk</td> <td>No losses to follow-up described. Analysed by intention to treat, but any events occurring after unblinding not recorded</td> </tr> </tbody> </table>			Bias	Authors' judgement	Support for judgement	Random sequence generation (selection bias)	Unclear risk	Women matched for diagnosis of chronic disease. From matched pairs, research nurse randomly selected which member would be assigned to which group. Method not described	Allocation concealment (selection bias)	Unclear risk	Not described	Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up described. Analysed by intention to treat, but any events occurring after unblinding not recorded
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Allocation concealment (selection bias)	Unclear risk	Not described												
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up described. Analysed by intention to treat, but any events occurring after unblinding not recorded												

Nachtigall 1979 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	States participants and research physicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States participants and research physicians blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Correlation for some baseline prognostic factors was low between individual pairs, but group means were similar.

Notelovitz 2002

Methods	<p>Stated purpose: to determine the lowest effective dose of an oestradiol transdermal delivery system for preventing bone loss in postmenopausal women</p> <p>Stratification: not described</p> <p>Unblinding: not described</p> <p>No. of women screened for eligibility: not stated</p> <p>No. randomised: 355 (0.025 mg dose: 89; 0.05 mg dose: 90; 0.075 mg dose: 89; placebo: 87)</p> <p>No. analysed: 355 (data imputed for losses to follow-up)</p> <p>Losses to follow-up: 34 (9.6%)</p> <p>Adherence to treatment: 125 drop-outs: 125 (35%) did not complete 2 years' treatment (88 in active treatment arms, 37 in placebo arm). One participant was withdrawn for failure to adhere to the treatment schedule. Overall level of adherence to treatment in women who continued with their allocated treatment is not described.</p> <p>Analysis by intention to treat: yes</p> <p>No. of centres: 22</p> <p>Years of recruitment: not stated</p> <p>Design: parallel</p> <p>Funding: Proctor and Gamble Pharmaceuticals</p>
Participants	<p>Included</p> <p>Postmenopausal, non-osteoporotic, ambulatory women younger than 70 years of age who had had a hysterectomy, with or without bilateral oophorectomy, at least 12 months earlier. Postmenopausal status documented by serum oestrogen < 23 picograms/mL and FSH serum levels > 40 mIU/mL. Non-osteoporotic status defined by dual energy x-ray absorptiometry (DXA) minimum T-score of -2.5</p> <p>Excluded</p> <p>Participants who had received oral oestrogens within 2 months of enrolment, or who had contraindications to oestrogen therapy or history of oestrogen intolerance, women with clinically significant systemic or psychiatric disorders; history of cancer (other than basal cell carcinoma in remission or uterine cancer treated by hysterectomy); history of osteomalacia, hyperparathyroidism or untreated hyperthyroidism, abnormal serum lipids, creatinine or liver enzymes; use of medications within 3 months of enrolment that could modify BMD, radiographic abnormalities of the lumbar spine on anterior/posterior or lateral view, which would preclude precise DXA measurements</p> <p>Mean age: not stated</p> <p>Age range: not stated</p> <p>Means of recruitment: not stated</p> <p>Baseline equality of treatment groups: yes</p> <p>Country: USA</p>
Interventions	HT arm: 2 patches, delivering daily dose of oestradiol: 0.025 mg, 0.05 mg or 0.075 mg

Notelovitz 2002 (Continued)

Control arm: 2 placebo patches
 Duration: 2 years (26 cycles)

Outcomes Breast cancer (regular mammograms)
 Fractures

Notes Power calculation: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	34 (9.6%) losses to follow-up. Analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blinded, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States double-blinded, double-dummy; "hard" outcomes
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

Obel 1993

Methods	Stated purpose: to compare combined and sequential therapy with respect to relief of climacteric symptoms, effects on the endometrium and on vaginal cellular maturation, steroid metabolism and side effects Stratification: not mentioned Unblinding: not described No. of women screened for eligibility: 176, of whom 21 unwilling to take placebo, 2 found not post-menopausal, 2 excluded for private reasons No. randomised: 151 (combined HT: 50, sequential HT: 50, placebo: 51) No. analysed: 129 (in the groups to which they were allocated) Losses to follow-up: 22 (11 from combined group, 5 from sequential group, 6 from placebo group) Adherence to treatment: not described Analysis by intention to treat: no No. of centres: 1 Years of recruitment: not stated Design: parallel Funding: Pharmaceutical Division, Novo Nordisk
Participants	Included

Obel 1993 (Continued)

Women in early menopause (last spontaneous vaginal bleeding > 6 and < 24 months earlier), no HT within preceding 24 months

Excluded

Women with previous or current oestrogen-dependant neoplasia, thromboembolic disease, liver or pancreatic disease, diabetes mellitus, severe obesity, disease with high or low bone turnover and medication known to influence bone metabolism or provoke induction of liver enzymes

Mean age: not stated

Age range: not stated

Means of recruitment: All 5800 women born between 1930 and 1933 in Frederiksborg County, Denmark, were invited to participate.

Baseline equality of treatment groups: yes

Country: Denmark

Interventions	HT arm Oral oestradiol 2 mg + norethisterone 1 mg Oral oestradiol 2 mg days 1-22 + norethisterone acetate days 13-22, then oestradiol 1 mg days 22-28 Control arm: placebo Duration: 2 years	
Outcomes	Only outcomes of interest to this review: endometrial cancer, quality of life	
Notes	Power calculation: not mentioned	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22 (15%) losses to follow-up for endometrial cancer (11 from combined group, 5 from sequential group, 6 from placebo group), analysed by ITT. However, only 70% of women included for quality of life outcomes (loss to follow-up rates similar across groups)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded - identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blinded - no further details
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Baseline quality of life scores on several measures appear substantially lower for placebo group.

PEPI 1995

Methods	<p>Stated purpose: to investigate effects of oestrogen-only and combined therapies on cardiovascular disease risk factors, as well as on endometrial status, breast changes, bone density, menopausal symptoms and quality of life factors</p> <p>Stratification: by clinical centre and hysterectomy status</p> <p>Blinding: participants, clinical and laboratory personnel blinded; medication packages visually indistinguishable</p> <p>Unblinding: unblinding officer at each trial centre or by phone call to co-ordinating centre; referral gynaecologist at each centre not directly involved with data collection or patient care; able to access treatment assignment for management of safety issues</p> <p>No. of women screened for eligibility: approximately 1460 (states that 60% of women screened were randomised)</p> <p>No. randomised: 875</p> <p>No. analysed: 847 (97%)</p> <p>Losses to follow-up: 28 (CEE-only group: 5/170, CEE + MPA sequential group: 5/174, CEE + MPA continuous group: 4/174, CEE + MPA sequential group: 5/178, placebo group: 9/174)</p> <p>Adherence to treatment: drop-out rate disproportionately high in women with a uterus assigned unopposed oestrogen: 55% had to discontinue assigned therapy, largely owing to endometrial hyperplasia. Of 847 women who attended 3-year follow-up, 75% with a uterus and 80% without a uterus had at least 80% adherence to treatment. (Note: 55% of women with a uterus assigned unopposed oestrogen were required to discontinue assigned therapy owing to endometrial hyperplasia.)</p> <p>Analysis by intention to treat: no - but 97% of women analysed by ITT</p> <p>No. of centres: 7</p> <p>Years of recruitment: December 1989–February 1990</p> <p>Design: parallel</p> <p>Funding: research grants from National Heart, Lung and Blood Institute, National Institute of Child Health and Human Development, National Institute of Health and Human Development, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Aging, USA</p>
Participants	Included
	<p>Healthy postmenopausal women 45–65 years of age, with or without a uterus; ceased menstruation 12 months before entry or had hysterectomy at least 2 months before entry and FSH levels < 40 mU/mL</p>
	Excluded
	<p>Women who had used hormones within past 3 months, women treated with thyroid hormone unless stabilised on treatment, serious illness including heart or thromboembolic disease, previous endometrial or breast cancer, contraindications to oestrogen</p> <p>Mean age: 56 years (SD 4)</p> <p>Age range: 45–64</p> <p>Means of recruitment: through mass media and community efforts</p> <p>Baseline equality of treatment groups: Women assigned to placebo had higher mean levels of fibrinogen and low density lipoprotein-C at baseline.</p> <p>Country: USA</p>
Interventions	HT arm: 1 of the following regimens
	<p>CEE 0.625 mg daily (unopposed oestrogen)</p> <p>CEE 0.625 mg daily plus MPA 10 mg daily for first 10 days (combined sequential treatment)</p> <p>CEE 0.625 mg plus MPA 2.5 mg daily (combined continuous treatment)</p> <p>CEE 0.625 mg plus MP 200 mg daily for first 12 days (combined sequential treatment)</p> <p>Control arm: placebo</p> <p>Duration: 3 years</p>
Outcomes	<p>Primary endpoints: biological markers, not relevant to this review; however, the following prespecified outcomes were also measured.</p> <p>Breast cancer</p> <p>Endometrial cancer</p> <p>Cardiovascular disease</p> <p>Thromboembolism</p>

PEPI 1995 (Continued)

Gallbladder disease

Notes	Power calculation: based on primary (biological) outcome: A sample of 840 women was projected to provide minimum power of 0.92 to detect differences of 5 mg/dL in HDL cholesterol for any pair-wise comparison of treatment arms at 3 years. 55% of women with a uterus assigned unopposed oestrogen were required to discontinue assigned therapy owing to endometrial hyperplasia.	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated blocks of variable length
Allocation concealment (selection bias)	Low risk	Allocation assignments on encrypted file loaded on computer at clinical centre and issued once eligibility confirmed (or by phone to co-ordinating centre in case of computer failure)
Incomplete outcome data (attrition bias) All outcomes	Low risk	28 (3%) lost to follow-up; 97% of women analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, clinical and laboratory personnel blinded; medication packages visually indistinguishable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical and laboratory personnel blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Placebo group had higher levels of fibrinogen and low-density lipoprotein C at baseline; otherwise, groups prognostically balanced

Tierney 2009

Methods	Stated purpose: to determine whether oestradiol and norethindrone HT prevents decline in delayed verbal recall in older women with normal to mildly impaired memory functioning Stratification: none reported Unblinding: adverse effects managed by data safety monitoring board, which did not have access to study participants No. of women screened for eligibility: 987 No. randomised: 142 No. analysed: 128 at 2 years Losses to follow-up: 14 (8 in HT group, 6 in placebo group) Adherence to treatment: 26 discontinued intervention in HT group, 16 discontinued in placebo group Analysis by intention to treat: no, but 128/142 analysed by ITT (90%) No. of centres: 1 Years of recruitment: 2000-2004 Design: parallel Funding: Canadian Institutes of Health Research, Institute of Neurosciences Mental Health and Addiction, Shire Biochemistry. Pharmaceutical companies provided tablets.
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Tierney 2009 (Continued)

	Included	
Participants	<p>Women at least 60 years of age, at least 12 months since last menstrual cycle, normal to below-normal scores on screening for short-delay verbal recall, fluent in English and with normal reading and hearing abilities</p>	
	Excluded	
	<p>Women with dementia or history of a condition that would affect cognition; women with conditions considered to be exacerbated by oestrogen, or taking specific medications (listed in the publication) including HT within past 2 years; women received neuropsychological testing to rule out dementia</p>	
	<p>Mean age: not stated</p>	
	<p>Age range: 61-87</p>	
	<p>Means of recruitment: advertisements, display booths (e.g. in hospitals, seniors' clubs), family physician referrals</p>	
	<p>Baseline equality of treatment groups: similar baseline scores</p>	
	<p>Country: Canada</p>	
Interventions	<p>HT group: 1 mg 17-B oestradiol daily for 4 days a week followed by 1 combined oestrogen/progestin ampoule (1 mg 17-B oestradiol and 0.35 mg norethindrone) per day for 3 days a week</p>	
	<p>Control: placebo</p>	
	<p>Duration: 2 years</p>	
	<p>All women were given the same intervention, whether or not they had a uterus.</p>	
Outcomes	<p>Short-delay verbal recall of the California Verbal Learning Test</p>	
	<p>Adverse events, including cardiovascular events, cancer, fractures</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Pharmacy allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% losses to follow-up by 2 years; those lost to follow-up did not differ on baseline short-delay recall scores from those who stayed in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study; placebo capsules were identical in appearance to the active capsule.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States that study personnel and participants were blinded - no specific statement about outcome assessment
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Tierney 2009 (Continued)

Other bias	Unclear risk	More women in HT group than in placebo group reported breast tenderness, vaginal bleeding and discharge, suggesting that they may have been aware that they were receiving HT.
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WAVE 2002

Methods	<p>Stated purpose: to determine whether HT or antioxidant vitamin supplements, alone or in combination, influence the progress of coronary artery disease in postmenopausal women, as measured by angiography</p> <p>Stratification: clinical centre, hysterectomy status</p> <p>Unblinding: adverse effects managed by gynaecologist not involved in outcome assessment who had access to treatment assignment if necessary, with permission of co-ordinating centre</p> <p>No. randomised: 211</p> <p>No. analysed: 206 for clinical status at end of study</p> <p>Losses to follow-up: 5 (3 in HT group, 2 in placebo group)</p> <p>Adherence to treatment: evaluated for 159/211 who had angiographic follow-up: HT group took 67% of medication, placebo group took 70%; 9/108 women in placebo group crossed to open-label oestrogen</p> <p>Analysis by intention to treat: no - but 98% of women analysed by ITT</p> <p>No. of centres: 7</p> <p>Years of recruitment: July 1997-August 1999</p> <p>Design: parallel</p> <p>Funding: National Heart, Lung and Blood Institute contract, General Clinical Research Center grant, USA</p>
Participants	<p>Included</p> <p>Postmenopausal women with 1 or more 15% to 75% coronary stenoses in an artery not subjected to intervention, seen on angiogram within 4 months of study entry. Postmenopausal defined as post bilateral oophorectomy, younger than 55 years of age with an FSH of 40 Mu/mL or higher or older than 55 years</p> <p>Excluded</p> <p>HT use within 3 months, concurrent use of more than 60 mg/d of vitamin C or 30 IU daily of vitamin E and unwilling to stop taking them; suspected breast, uterine or cervical cancer; uncontrolled diabetes or hypertension, MI within 4 weeks, elevated triglycerides or creatinine levels, symptomatic gallstones, heart failure, history of haemorrhagic stroke, bleeding diathesis, PE, DVT or untreated osteoporosis</p> <p>Mean age: 65</p> <p>Age range: 56-74</p> <p>Means of recruitment: recruited at clinical sites in USA and Canada</p> <p>Baseline equality of treatment groups: higher prevalence of diabetes and higher fasting blood glucose levels in the HT group</p> <p>Countries: USA and Canada</p>
Interventions	<p>HT arm: 1 of the following regimens</p> <p>CEE 0.625 (oestrogen-only therapy) - for women who had had a hysterectomy</p> <p>CEE 0.625 and MPA 2.5 mg daily (continuous combined therapy) - for women who had not had a hysterectomy</p> <p>Control arm: placebo</p> <p>Duration: 3 years</p> <p>In addition, this study included women who were prescribed a regimen of vitamins E and C or placebo vitamins. The only comparison considered in this review was HT/placebo vitamins vs placebo HT/placebo vitamins.</p>
Outcomes	<p>Primary outcome biological: change in minimum lumen diameter of qualifying coronary lesions</p> <p>Outcomes of interest to review</p> <p>All-cause death</p>

WAVE 2002 (Continued)

	Total mortality Cardiovascular events Venous thromboembolism Stroke Breast cancer Quality of life	
Notes	Study publication pools results for women receiving unopposed and combined therapies. Power calculation: based on primary (biological) outcome: 423 women provide 90% power to detect an effect size of at least 0.33 (corresponding to a change in minimum lumen diameter of 0.1 mm and assuming 20% of women would not undergo a follow-up angiogram)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-randomised, permuted block design with random blocks of 2 and 4
Allocation concealment (selection bias)	Low risk	Remotely by phone call to study co-ordinating centre
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 5 (3 in HT group, 2 in placebo group); 98% of women analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators and staff at clinical centres blinded, except (when necessary) the study gynaecologist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators and staff at clinical centres blinded - main outcomes "hard"
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Active group had higher prevalence of diabetes and higher fasting blood glucose levels; otherwise, groups were prognostically balanced.

WEST 2001

Methods	<p>Stated purpose: to determine whether 17B-oestradiol reduces risk of recurrent stroke or death among postmenopausal women who have experienced a transient ischaemic attack or a non-disabling ischaemic stroke</p> <p>Stratification: by trial centre and risk level (3 levels)</p> <p>Unblinding: study internist unblinded in the case of overriding concern about a woman's clinical care</p> <p>No. of women screened for eligibility: 5296 (2772 ineligible, 1843 declined to participate, 17 unable to be randomised within protocol time frame)</p> <p>No. randomised: 664 (HT: 337, placebo: 327)</p> <p>No. analysed: 664</p> <p>Losses to follow-up: nil</p> <p>Adherence to treatment: 34% of the oestradiol group and 24% of the placebo group dropped out. Non-adherence to allocated treatment: overall mean: HT group: 44%; placebo: 36%. Among women who continued with treatment, adherence to treatment was 90% in both groups.</p> <p>Analysis by intention to treat: yes</p>
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WEST 2001 (Continued)

No. of centres: 21 (single recruitment hub)
 Years of recruitment: December 1993-May 1998
 Design: parallel
 Funding: National Institute of Neurological Disorders and Stroke grant, Medical Research Council of Canada grant. Mead Johnson Laboratories provided support and study drug.

Participants	Included	
	Postmenopausal women (i.e. amenorrhoea for at least 12 months, or having undergone hysterectomy and > 55 years of age) over 44 years of age within 90 days of a qualifying ischaemic stroke or transient ischaemic attack	
	Excluded	
	Women whose index event was disabling or occurred while taking oestrogen; women with history of breast or endometrial cancer, who had had a venous thromboembolic event while receiving oestrogen replacement therapy, had had a neurological or psychiatric disease that could complicate evaluation of endpoints or had a coexisting condition that limited life expectancy	
	Mean age: 71	
	Age range: 46-91	
	Means of recruitment: admissions to 20 largest regional hospitals in Connecticut and Massachusetts; also via contact with selected neurology groups and direct referral from physicians	
	Baseline equality of treatment groups: yes	
	Country: USA	
Interventions	HT arm: 17-beta oestradiol 1 mg daily plus, for women with a uterus, a course of medroxyprogesterone acetate once a year, 5 mg daily for 12 days Control arm: placebo Duration: 2.8 years	
Outcomes	Death or recurrent stroke Myocardial infarction Cognitive function	
Notes	Study publication pools results for women receiving unopposed and combined therapies. Power calculation: 652 women required to give 80% power to detect a reduction in the rate of death or non-fatal stroke from 25% in the placebo group to 15% in the HT group (2-tailed P = 0.05)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated at pharmacy, in blocks of 4
Allocation concealment (selection bias)	Low risk	By remote contact with trial pharmacy
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up; analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint assessors blinded

WEST 2001 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

WHI 1998

Methods	<p>Stated purpose: to test the hypothesis that women taking HT will have lower rates of coronary heart disease and osteoporosis-related fractures</p> <p>COMBINED HT ARM:</p> <p>Stratification: by clinical centre site and age group</p> <p>Re blinding: all participants, clinic staff and outcome assessors blinded, with the exception of 331 participants who were unblinded from the unopposed oestrogen arm and were reassigned to the combined HT arm owing to change in the protocol (see Notes). A further 432 women (248 in the experimental arm and 183 in the placebo arm) had a hysterectomy after randomisation (for reasons other than cancer) and were switched to unopposed oestrogen or corresponding placebo in the unopposed oestrogen study arm.</p> <p>Unblinding: when required for safety or symptom management, unblinding officer, unblinded clinical gynaecologist, who was not involved with outcomes assessment. At average 5.2-year follow-up, 3444 women in experimental group and 548 women in placebo group had been unblinded, mainly to manage persistent vaginal bleeding.</p> <p>No. randomised: 16,608 (8506 to experimental group, 8102 to placebo group)</p> <p>No. analysed: 16,608</p> <p>Losses to follow-up: 583 participants (3.5%) - i.e. no outcome data for > 18 months: 307 in HT arm (3%), 276 in control group (3.5%). Vital status known for 96.5%</p> <p>Drop-outs/Non-adherence to allocated treatment: Women with adherence to treatment less than 80% (by pill count) were counted as drop-outs. Drop-out rates at 5.6 years were 42% in the experimental arm and 38% in the placebo group. In addition, 10.7% of women in the placebo group crossed to receive active treatment.</p> <p>Analysis by intention to treat: yes (analysed with and without unblinded group in experimental arm)</p> <p>No. of centres: 40</p> <p>Power calculation: Sample gives 80%-95% power for primary endpoint comparisons at 5% significance, assuming an intervention effect of 20% for CHD and 21% for combined fractures at 6-9 year follow-up, and an intervention effect of 22% for breast cancer at 14-year follow up (risk ratio of 1.3 assumed for increased risk of breast cancer in intervention group).</p> <p>Years of recruitment: 1993-1998</p> <p>Note: planned 8.5 years' follow-up. Trial was stopped after mean of 5.6 years, as test statistic for breast cancer exceeded predetermined stopping boundary, and global risk index indicated risks exceeding benefits.</p> <p>This study continued follow-up for breast cancer outcomes beyond the planned trial completion date for women who consented to continue follow-up (n = 12,788: 83% of those eligible, of whom 2.7% dropped out (Manson 2013)). Seventeen percent of surviving women declined to be re-consented, and their data were censored for the additional follow-up period. Baseline characteristics were evenly distributed between the 2 groups.</p> <p>WHI 1998 UNOPPOSED OESTROGEN ARM:</p> <p>Stratification: as above</p> <p>Blinding: as above</p> <p>Unblinding: as above</p> <p>No. randomised: 10,739 (including 248 in experimental arm, 183 in placebo arm) joined this study after randomisation to corresponding arms in WHI 2002 and having subsequently had hysterectomy (for reasons other than cancer).</p> <p>No. analysed: 10,739</p> <p>Losses to follow-up: 563</p> <p>Drop-outs/Non-adherence to allocated treatment: Women with adherence to treatment of under 80% by pill count were counted as dropouts. The drop-out rate was 53.8% by the end of the study (6.8 years) and did not vary significantly between study arms. In addition, 9.1% of women in the placebo arm and</p>
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WHi 1998 (Continued)

5.7% in the active treatment group initiated hormone use outside of the study through their own physician.

Analysis by intention to treat: yes

No. of centres: 40

Power calculation: 12,375 participants needed to detect a 21% reduction in CHD rates over projected 9-year average follow-up

Years of recruitment: 1993-1998

N.B. This arm of [WHi 1998](#) was stopped early after a mean follow-up of 7.1 years (planned for 9), when it was determined that the prospect of obtaining more precise evidence about effects of the intervention was unlikely to outweigh potential harms, although no predefined safety boundaries had been crossed. This study continued follow-up for all outcomes beyond the planned trial completion date for women who consented to continue follow-up ($n = 7645$; 78% of those eligible, of whom 3% dropped out). Twenty-two percent of surviving women declined to be re-consented, and their data were censored for the additional follow-up period. Baseline characteristics were similar in the 2 groups, and imputation analyses suggested that this loss to follow-up did not significantly influence study findings.

WHIMS ANCILLARY STUDY:

[WHi 1998](#) enrolled 7479 participants who were free of probable dementia and were 56-79 years of age. Of these, 4532 were from the combined HT arm of [WHi 1998](#) [[WHi 1998](#) (WHIMS:combined arm) and 2947 were from the unopposed oestrogen arm [[WHi 1998](#) (WHIMS:unopposed oestrogen arm)]. Overall, 92.4% of eligible women participated.

Years of recruitment: May 1996-December 1999

Analysis by intention to treat: all analysed by ITT for planned primary and secondary outcomes. For a third outcome (global cognitive function), which was not formally preplanned, 178 participants (3.9%) were excluded from the combined arm (151 because relevant follow-up data were missing, and 27 because they consented to join WHIMS more than 6 months after WHi treatment assignment, by which time treatment effects may already have been under way), and 139 (4.7%) were excluded from the unopposed oestrogen arm (109 owing to missing follow-up data and 30 as the result of enrolment 6 months or more after randomisation).

Adherence to allocated treatment (i.e. proportion taking > 80% of study medication): unopposed oestrogen arm: year 1: 77.2% in HT group vs 84.1% in placebo group; year 6: 42% in HT group vs 47.8% in placebo group; combined HT arm: year 1: 71% in HT group vs 83% in the placebo group; year 4: 49% in HT group vs 61% in placebo group.

Power: designed to provide > 80% power to detect an observed 40% relative reduction in the incidence rate of clinically diagnosed all-cause dementia

Duration: Mean time from randomisation to [WHi 1998](#) to the last WHIMS cognitive screening examination was 4.05 years for women in the combined HT arm and 5.21 years for women in the unopposed oestrogen arm.

WHISCA ANCILLARY STUDY

Randomised in 1999

Enrolled 2304 women who had been enrolled in WHIMS for a mean of 3 years (1106 women from WHIMS: combined arm; 886 from WHIMS: unopposed oestrogen arm)

Re-randomised in 2004-2005 for further follow-up to September 2007; 84% of the original cohort agreed to continue ($n = 1933$). Those who participated were more likely than those who did not to be younger, non-smokers, free of diabetes and cardiovascular disease and prior users of oral contraceptives, and to have higher MMSE scores. Among ongoing participants, active and placebo groups had similar characteristics.

Participants	COMBINED HT ARM Included Postmenopausal women (no vaginal bleeding for 6 months, or for 12 months for 50-54 year olds; any use of postmenopausal hormones), with a uterus, aged 50-79 at initial screening, likely to reside in area for 3 years, provision of written informed consent Excluded
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WHI 1998 (Continued)

Medical condition predictive of survival time < 3 years, invasive cancer in past 10 years (except non-melanoma skin cancer), breast cancer at any time or suspicion of breast cancer at baseline screening, acute myocardial infarction, stroke, transient ischaemic attack in previous 6 months, known chronic active hepatitis or severe cirrhosis, blood counts indicative of disease, severe hypertension or current use of oral corticosteroids, femoral neck bone mineral density more than 3 standard deviations below the corresponding age-specific mean, endometrial cancer or endometrial hyperplasia at baseline, malignant melanoma, pulmonary embolism or deep vein thrombosis that was non-traumatic or had occurred in the previous 6 months, bleeding disorder, lipaemic serum and hypertriglyceridaemia diagnosis, current use of anticoagulants or tamoxifen, PAP smear or pelvic abnormalities, unwillingness or inability to complete baseline study requirements, alcoholism, drug dependency, mental illness, dementia, severe menopausal symptoms inconsistent with assignment to placebo, inability or unwillingness to discontinue current HT use or oral testosterone use, inadequate adherence with placebo run-in, unwillingness to have baseline or follow-up endometrial aspirations, active participant in another randomised clinical trial

Mean age: 63 years (SD 7)

Age range: 50-79. Age ratio of 33%:45%:21% for baseline age categories of 50-59, 60-69 and 70-79, respectively (enrolment targeted to achieve ratio of 30:45:25)

Recruitment: letter of invitation in conjunction with media awareness programme. Sampling method gave women from minority groups 6-fold higher odds of selection than Caucasian women and resulted in a sample with 84% racially/ethnically designated "white", and 16% non-"white"

Screening: Interested women were screened by phone or mail for eligibility, then attended 3 screening visits for history, clinical exam and tests. Three-month washout period before baseline evaluation of women using postmenopausal hormones at baseline screening. Lead-in placebo pills given for at least 4 weeks during screening process to establish compliance with pill taking

Baseline equality of treatment groups: no substantive differences between study groups at baseline

Country: USA

UNOPPOSED OESTROGEN ARM
Included

Postmenopausal women who had undergone hysterectomy (therefore considered postmenopausal for enrolment purposes), aged 50-79 at initial screening, likely to reside in area for 3 years, provision of written informed consent

Excluded

As above

Mean age: 64

Age range: 50-79.

Age ratio of 33%:45%:21% for baseline age categories of 50-59, 60-69 and 70-79, respectively (enrolment targeted to achieve ratio of 30:45:25)

Recruitment: as above

Screening: as above

Baseline equality of treatment groups: no substantive differences between study groups at baseline

Country: USA

WHIMS ancillary study
Included

Participants in either arm of [WHI 1998](#), at least 65 years of age and free of probable dementia

WHISCA ANCILLARY STUDY

Women from 14 of the WHIMS clinical sites

Interventions
COMBINED HT ARM

Experimental group: combined oestrogen and progesterone as 1 daily tablet containing conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg

Control group: matching placebo

Duration: 5.6 years (mean duration of treatment)

WHi 1998 (Continued)

Permanent discontinuation of medication: women who developed breast cancer, endometrial hyperplasia not responsive to treatment, endometrial atypia, endometrial cancer, deep vein thrombosis, pulmonary embolus, malignant melanoma, meningioma, triglyceride level over 1000 mg/dL, prescription of oestrogen, testosterone or selective oestrogen-receptor modulators by their personal physician
 Temporary discontinuation of medication: women who had acute MI, stroke, fracture, major injury involving hospitalisation, surgery involving anaesthesia, illness resulting in immobilisation for longer than 1 week, other severe illness for which hormone use is temporarily inappropriate

N.B. **WHi 1998** (WHIMS) investigators reported outcomes according to study arm (unopposed oestrogen or combined HT therapy) and also (as per protocol) reported results pooled across the 2 arms. However, results showed significant baseline prognostic differences between the 2 arms (see Quality Table). We have not pooled the results in this review.

UNOPPOSED OESTROGEN ARM

Experimental group: 0.635 mg CEE daily

Control arm: placebo

Permanent discontinuation of medication: as above

WHIMS ANCILLARY STUDY

As for either arm of **WHi 1998** above

Outcomes	COMBINED HT ARM Cardiovascular disease: acute MI, silent MI, coronary death, stroke, pulmonary embolus Cancer: breast, colorectal, endometrial, other cancers Fractures: hip, vertebral, osteoporotic UNOPPOSED OESTROGEN ARM As above (with the exception of endometrial cancer) WHIMS ANCILLARY STUDY Cognitive function Mild cognitive impairment Dementia For assessment of outcomes, women in WHIMS underwent up to 4 phases of testing as follows. 1. Participants underwent cognitive screening with the Modified MMSE at baseline and annually. 2. Women who scored below an education-adjusted cut-off point proceeded to a battery of psychoneurological tests and standardised interviews, plus interviews with a designated informant (friend or relative). 3. Clinical assessments by local physicians. 4. CT and blood tests to rule out reversible pathology. All cases judged locally as probable dementia were independently evaluated by 2 adjudicators blinded to the diagnosis, as were 50% of cases of mild cognitive impairment and 10% of all cases without dementia. Mild cognitive impairment defined as per current DSM IV criteria - operationally defined as follows: poor performance (< 10th percentile) on a battery of neuropsychological tests, report of mild functional impairment from designated informant, no evidence of a psychiatric or medical explanation for the cognitive decline, absence of dementia Dementia defined as per DSM-IV criteria
Notes	N.B. The original WHI protocol allowed women with a uterus to be randomised to receive unopposed oestrogen. As evidence emerged (from the PEPI trial) that this could be unsafe, 331 participants with a uterus in the intervention group in the unopposed oestrogen arm were reassigned to the intervention group in the combined HT arm. Both arms closed early: Combined arm at 5.6 years (8.5 planned); oestrogen-only arm at 6.8 years (9 planned)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised by permuted block algorithm

WHI 1998 (Continued)

Allocation concealment (selection bias)	Low risk	By local access to remote study database
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Combined HT arm: 583 participants (3.5%) lost to follow-up. Vital status known for 96.5%</p> <p>For 11-year breast cancer outcomes in the combined HT arm, 17% of women had withdrawn. Imputation analyses and comparison of baseline characteristics suggested that this did not significantly influence effect estimates.</p> <p>Oestrogen-only arm: 563 (5%) - analysed by intention to treat</p> <p>WHISCA: for ongoing follow-up (2004-2007), 16% of women withdrew. Clinical and demographic characteristics of those continuing differed from those discontinuing, but active and placebo groups did not differ significantly.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinic staff were blinded, with the exception of 331 participants who were unblinded from the unopposed oestrogen arm and reassigned to the combined HT arm owing to a change in protocol.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	<p>In the unopposed oestrogen arm, greater use of aspirin at bedtime in the placebo group at baseline</p> <p>In the combined HT arm, lower prevalence of stroke and higher percentage of participants using statins in the active treatment group at baseline</p>

WISDOM 2007

Methods	<p>Stated purpose: to assess long-term benefits and risks of HT</p> <p>Stratification: by hysterectomy status and intended use of HT: women with no uterus and unwilling to take placebo randomised to CEE or combined HT. Equal probability of any treatment within each stratum</p> <p>No. of women screened for eligibility: 14,203</p> <p>No. randomised: 4385; 2196 on combined therapy, 2189 on placebo (see Notes)</p> <p>No. analysed: 4385</p> <p>Losses to follow-up: 5</p> <p>Adherence to treatment: 615 (14%) had dropped out from randomised treatment by trial closure. Trial treatment delivered 73% of time to women in combined HT arm and 86% of time to women on placebo</p> <p>Analysis by intention to treat: yes</p> <p>No. of centres: 384 UK, 91 Australian and 24 New Zealand general practitioner practices</p> <p>Years of recruitment: 1999-2002</p> <p>Design: parallel</p> <p>Funding: non-commercial medical research funding</p>
Participants	<p>Included</p> <p>Postmenopausal women 50-69 years of age</p> <p>Excluded</p>

WISDOM 2007 (Continued)

History of breast cancer, any other cancer in past 10 years except basal or squamous cell skin cancer, endometriosis or endometrial hyperplasia, venous thromboembolism, gallbladder disease, MI, unstable angina, cardiovascular accident, subarachnoid haemorrhage, transient ischaemic attack, use of HT within past 6 months, unlikely to be able to give informed consent

Mean age: 63

Age range: 50-69

Means of recruitment: general practitioner practice registers

Countries: UK, Australia, New Zealand

Interventions	<p>HT arm: daily CEE 0.625 mg plus medroxyprogesterone acetate 2.5 mg (for women with or without a uterus), or daily CEE 0.625 (for women without a uterus) Control arm: placebo Duration: planned for median 10 years, but prematurely closed after median 11.9 months (range 7.1-19.6)</p> <p>Women with a uterus within 3 years of last period, those aged 50-53 and older women with unacceptable breakthrough bleeding took medroxyprogesterone acetate 5.0 mg.</p> <p>Women with a uterus who experienced unacceptable spotting or bleeding on the above therapy were offered open-label CEE 0.625 mg plus medroxyprogesterone acetate 10.0 mg daily for the last 14 days of a 28-day cycle.</p> <p>All women took placebo medication during run-in: Those who achieved 80% compliance were randomised.</p> <p>A further 1307 women were randomised to a comparison of oestrogen-only vs combined HT: These results are not reported here.</p>
Outcomes	<p>Major cardiovascular disease (primary) Osteoporotic fractures (primary) Breast cancer Mortality VTE CVD Dementia (no follow-up data collected) Adverse events</p> <p>Quality of life (reported among 3721 women with an intact uterus or subtotal hysterectomy, among whom 1862 were randomised to combined HT and 1859 to placebo). A variety of overall and symptom-specific measures were used, including EuroQoL-5D (which measures health-related quality of life) and a generic VAS scale (which measures quality of all aspects of life) - only these 2 measures are included in this review</p>
Notes	<p>Powered in protocol to detect 25% reduction in CHD over 10 years - this assumed an 18,000 sample size, but trial stopped early with 26% of target</p> <p>A further 1307 women were included in comparison of combined therapy vs oestrogen only and were not included in this review.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remote computer-generated
Allocation concealment (selection bias)	Low risk	Remote computer-generated
Incomplete outcome data (attrition bias)	Low risk	615 (14%) had withdrawn from randomised treatment by trial closure; analysed by intention to treat

WISDOM 2007 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinic staff blinded except when vaginal bleeding triggered a code break
Blinding of outcome assessors (detection bias) All outcomes	Low risk	All outcome assessors blinded except when vaginal bleeding triggered a code break
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

Yaffe 2006

Methods	<p>Stated purpose: to investigate effects of unopposed ultra-low-dose transdermal oestradiol on cognition and health-related quality of life in postmenopausal women</p> <p>Stratification: by clinical centre</p> <p>No. of women screened for eligibility: 1509 (of whom 605 had 1-week run in phase. 10/605 were non-compliant and 1678 were found ineligible or refused to continue screening)</p> <p>No. randomised: 417 (treatment group: 208; placebo group: 209)</p> <p>No. analysed: using a time × treatment interaction. 388 at year 1, 376 at year 2</p> <p>Losses to follow-up: 40</p> <p>Adherence to treatment: drop-outs: 41. Among those who completed treatment, 84% used at least 75% of study drug during the entire 2 years.</p> <p>No. of centres: 9</p> <p>Years of recruitment: 1999-2000</p> <p>Design: parallel</p> <p>Funding: industry funded</p>
Participants	<p>Included</p> <p>Women 60-80 years of age with intact uterus, at least 5 years post menopause, normal bone density</p> <p>Excluded</p> <p>Women with unexplained uterine bleeding, endometrial hyperplasia, endometrium >mm double thickness on ultrasonography, abnormal mammogram suggestive of breast cancer, history of metabolic bone disease, cancer, coronary disease, stroke, transient ischaemic attack, VTE, uncontrolled hypertension, uncontrolled thyroid disease, liver disease, abnormal fasting triglyceride or fasting glucose, ever taken fluoride, calcitonin or bisphosphates, oestrogen or progestin within past 3 months</p> <p>Median age: 67</p> <p>Means of recruitment: not stated</p> <p>Baseline equality of treatment groups: mean MMSE scores slightly higher in intervention group ($P = 0.04$)</p> <p>Country: USA</p>
Interventions	<p>HT arm: oestradiol patch delivering approx 0.014 mg oestradiol daily, applied to abdomen weekly</p> <p>Control arm: identical placebo patch</p> <p>Duration: 2 years</p> <p>All participants also received 400 mg calcium twice daily and 400 IU vitamin D daily.</p>
Outcomes	<p>Preplanned secondary outcomes</p> <p>Changes in global cognition (MMSE)</p>

Yaffe 2006 (Continued)

Short-Form Health Survey (SF-36): Physical Component Scale and Mental Component Scale
 Bone mineral density was primary outcome (not reported here).

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remotely by computer
Allocation concealment (selection bias)	Low risk	By pharmacy
Incomplete outcome data (attrition bias) All outcomes	Low risk	40/417 (9.5%) women lost to follow-up; analysed by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

Abbreviations

- BMD: bone mineral density.
 BMI: body mass index.
 CEE: conjugated equine oestrogen.
 CHD: coronary heart disease.
 CVD: cardiovascular disease.
 DM: diabetes mellitus.
 DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
 DVT: deep vein thrombosis.
 DXA: dual-energy X-ray absorptiometry.
 EuroQol-5D: quality of life questionnaire.
 ET: oestrogen therapy.
 FSH: follicle-stimulating hormone.
 Ham D: Hamilton Depression Rating Scale.
 HDL: high-density lipoprotein.
 HT: hormone therapy.
 ITT: intention to treat: analysis of all randomised participants in the groups to which they were randomised.
 IU: International Units.
 LDL: low-density lipoprotein.
 mg: milligram.
 mL: millilitre.
 MI: myocardial infarction.
 MMSE: Mini Mental State Examination.
 MP: micronised progesterone.
 MPA: medroxyprogesterone acetate.

mu: milliunits.

PE: pulmonary embolism.

RCT: randomised controlled trial.

SD: standard deviation.

VAS: visual analogue scale.

VTE: venous thromboembolism.

WHI: Women's Health Initiative.

WHIMS: Women's Health Initiative Memory Study.

Definitions

Adherence to treatment refers to the number of tablets actually taken, which is often assessed by pill counts (see Additional Table 2).

Drop-outs: Participants who stopped their allocated treatment (and in some cases changed to a different off-trial treatment) but have known clinical outcomes and were included in the analysis.

Intention to treat: Analysis of all randomised participants in the groups to which they were randomised.

Losses to follow-up: Participants for whom outcomes of interest were unknown (and who may or may not have had outcomes imputed by statistical analysis).

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
AHT 2015	Not blinded
Aitken 1971	No outcomes of interest measured
Aitken 1973	No outcomes of interest measured
Angerer 2000	Duration less than 1 year
Bloch Thomsen 2002	No outcomes of interest measured
Chen 2001	No placebo, no outcomes of interest measured
Christiansen 1981	No outcomes of interest measured
Corrado 2002	No placebo, no outcomes of interest measured
Corson 1999	No placebo, no outcomes of interest measured
de Roo 1999	No outcomes of interest measured
Eiken 1996	No outcomes of interest measured
Estratab 1977	No outcomes of interest measured
EWA 2000	No placebo, no outcomes of interest measured
Genant 1990	No outcomes of interest measured
Graser 2001	Duration less than 1 year, no outcomes of interest measured
HABITS 2004	Not double-blinded
Haines 2003	No outcomes of interest measured
Hall 1998	Not double-blinded
Jensen 1985	No outcomes of interest measured

Study	Reason for exclusion
Kuopio 1998	Not blinded
Lufkin 1992	No outcomes of interest measured
Maki 2004	No outcomes of interest measured
Mizunuma 2010	No comparisons of interest comparing HT vs placebo only
Newhouse 2000	Duration less than 1 year
Ng 1992	No outcomes of interest measured
Nielsen 2006	No outcomes of interest measured
Ory 1998	No outcomes of interest measured
Os 2002	No placebo, no outcomes of interest measured
Paoletti 2015	No outcomes of interest measured
Papworth 2002	No placebo
Pefanco 2007	No outcomes of interest measured
Post 2001	No outcomes of interest measured
Rasgon 2014	No placebo group, interim outcomes measured
Saitta A 2001	Duration less than 1 year
Sanchez-Guerrero 2007	No outcomes of interest measured
Schierbeck 2012	Not blinded
SMART 2016	Co-intervention (bazedoxifene) in the HT group
Steiner 2007	Combines EPAT and WELL-HART data. No outcomes of interest measured
Teede 2002	No outcomes of interest measured
ULTRA 2005	No outcomes of interest measured
Virtanen 1999	Duration less than 1 year, no outcomes of interest measured
Wharton 2011	Planned duration of 1 year. Owing to high drop-out rate, results were reported only at 3 months.

DATA AND ANALYSES

Comparison 1. Women without major health problems (selected outcomes: death, CVD, cognition, QOL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from any cause: oestrogen-only HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oestradiol 1 mg (low dose) for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
1.2 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
1.3 CEE 0.625 mg (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.13]
2 Death from any cause: combined HT	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.76, 2.27]
2.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.71, 1.56]
2.3 CEE 0.625 mg (mod dose) + P (as per footnotes) for 3 years	3	18075	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.46]
2.4 CEE 0.045 mg (lowish dose) + 200 mg sequential progesterone for 4 years	1	505	Risk Ratio (M-H, Fixed, 95% CI)	3.58 [0.15, 87.57]
2.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.19]
2.6 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.93, 1.20]
2.7 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended fol- low-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
3 Death from any cause: oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.77]
4 Death from coronary heart disease: oe- strogen-only HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oestradiol 1 mg (low dose) daily for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
4.2 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.69, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 CEE 0.625 mg (mod dose) after 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.19]
5 Death from coronary heart disease: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.68, 1.66]
5.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.72, 1.38]
6 Death from coronary heart disease: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 1 mg 17-B-oestradiol (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.27]
7 Death from stroke: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 CEE 0.625 mg (low dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.58, 2.32]
8 Death from stroke: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 1 mg 17-B-oestradiol (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 74.46]
9 Death from stroke: combined continuous HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for median 1 year	1	4385	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [0.12, 73.37]
9.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.46, 2.35]
10 Death from colorectal cancer: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.66, 2.46]
11 Death from breast cancer: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Death from breast cancer: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 CEE 0.625 mg (mod dose) after median 11.8 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.15, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Death from colorectal cancer: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.40, 2.29]
13.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 7.1 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.52, 1.96]
13.3 CEE 0.0625 mg (mod dose) + MPA 2.5 mg after 11.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.80, 2.14]
14 Death from lung cancer: oestrogen-only HT (moderate dose)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Death from lung cancer (non-small cell or small cell)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.65, 1.70]
14.2 Death from non-small cell lung cancer	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.50]
14.3 Death from small cell lung cancer	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.62, 6.79]
15 Death from lung cancer: combined continuous HT (moderate dose)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Death from lung cancer (non-small cell or small cell) at mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.18, 2.55]
15.2 Death from non-small cell lung cancer at mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.24, 2.93]
15.3 Death from small cell lung cancer at mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.48, 2.81]
15.4 Death from lung cancer (any type) at median 14 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.88, 1.39]
16 Death from lung cancer: combined sequential HT (low dose oestrogen)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 1 mg 17-B-oestradiol (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 74.46]
17 Death from any cancer: combined continuous HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 CEE 0.625 mg daily (mod dose) + MPA 2.5 mg for 3 years	1	777	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.11, 67.80]
17.2 CEE 0.625 mg daily (mod dose) + MPA 2.5 mg for mean 5.2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.87, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Coronary events (MI or cardiac death): oestrogen-only HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Oestradiol 1 mg (low dose) for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.43]
18.2 CEE 0.625 mg (mod dose) for 3 years	1	349	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.12, 72.72]
18.3 CEE 0.625 mg (mod dose) for mean 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
18.4 CEE 0.65 (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
19 Coronary events (MI or cardiac death): combined continuous HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.15, 3.10]
19.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.05, 2.12]
19.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years	2	17385	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.07, 1.98]
19.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.95, 1.44]
19.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.22]
20 Coronary events (MI or cardiac death): combined sequential HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	352	Risk Ratio (M-H, Fixed, 95% CI)	4.89 [0.24, 101.09]
20.2 1 mg (low dose) 17-B-oestradiol daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.27]
20.3 Oestradiol patch 0.05 mg (mod dose) + 200 mg sequential progesterone for 4 years	1	497	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.15, 90.70]
21 Coronary events (MI or cardiac death): oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.16]

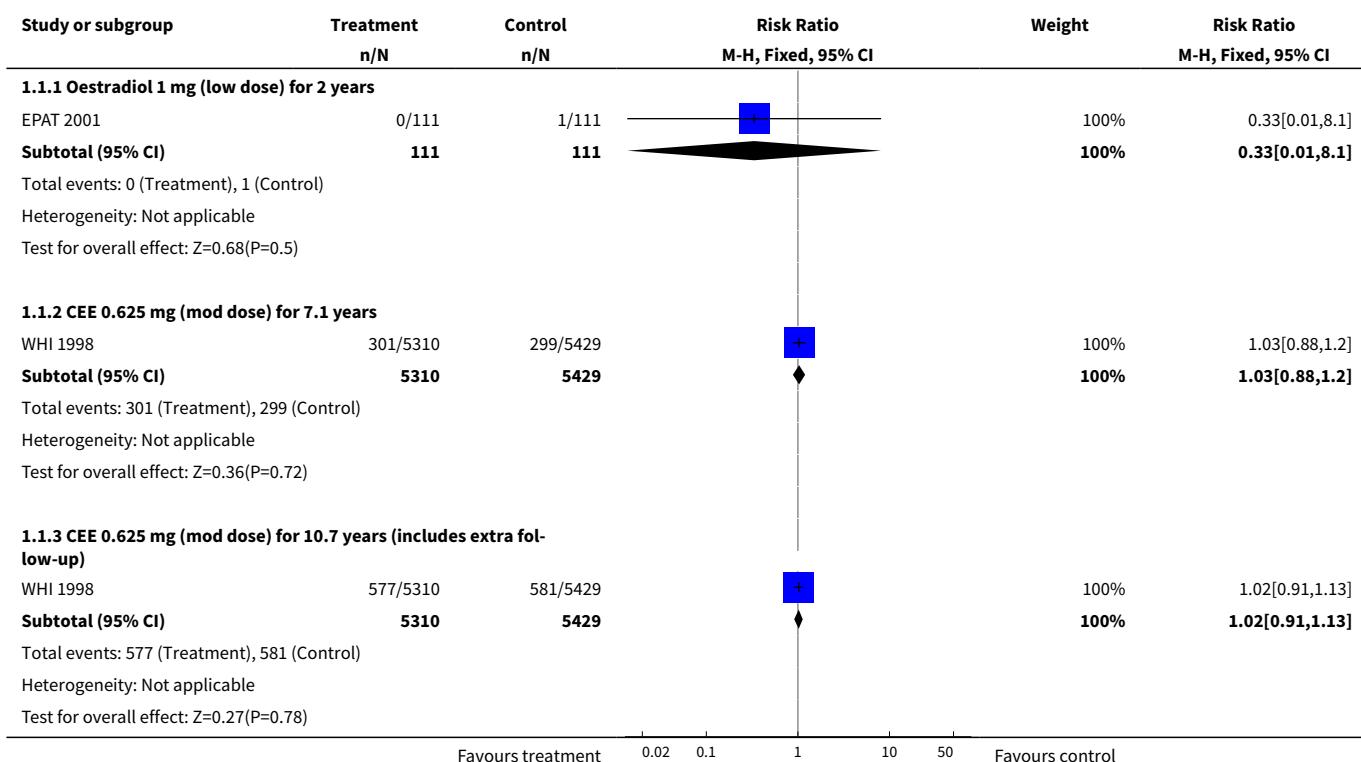
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Stroke: unopposed oestrogen	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Oestradiol 1 mg (low dose) for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.86]
22.2 CEE 0.625 mg (mod dose) for mean 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.06, 1.67]
22.3 CEE 0.625 mg (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.97, 1.40]
23 Stroke: combined continuous HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 1 year	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.49, 1.86]
23.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.83, 2.06]
23.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years	2	17385	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.02, 2.09]
23.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.09, 1.77]
23.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.06, 1.56]
23.6 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.33]
24 Stroke: combined sequential HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 1 mg (low dose) 17-B-oestradiol daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 74.46]
24.2 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.14]
25 Stroke: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	352	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.51]
26 Transient ischaemic attack: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Oestradiol 1 mg (low dose) for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.86]
27 Transient ischaemic attack: combined sequential HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 1 mg 17-B-oestradiol (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 16.13]
27.2 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.14]
28 Transient ischaemic attack: oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.44]
29 Stroke or transient ischaemic attack	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	1	4385	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.37, 1.46]
30 Venous thromboembolism (DVT or PE): oestrogen-only HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 CEE 0.625 mg (mod dose) for up to 2 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.12, 4.39]
30.2 CEE 0.625 mg (mod dose) for 3 years	1	349	Risk Ratio (M-H, Fixed, 95% CI)	6.96 [0.36, 133.75]
30.3 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.00, 1.74]
30.4 CEE 0.625 mg (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
31 Venous thromboembolism (DVT or PE): combined sequential HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 1 mg 17-B-oestradiol (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 74.46]
31.2 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.14]
31.3 CEE 0.045 mg (lowish dose) + 200 mg sequential progesterone for 4 years	1	505	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.02, 9.73]

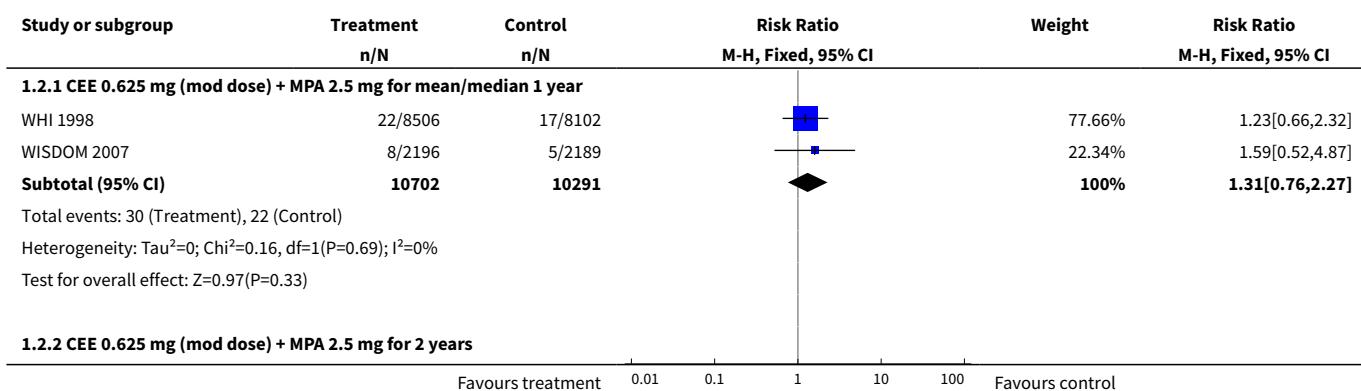
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.4 Oestradiol patch 0.05 mg (mod dose) + 200 mg sequential progesterone for 4 years	1	497	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.08, 19.69]
32 Venous thromboembolism (DVT or PE): combined continuous HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	4.28 [2.49, 7.34]
32.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [1.88, 4.71]
32.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.73, 3.72]
32.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.55, 2.64]
32.5 CEE 0.625 mg (mod dose) + 2.5 mg MPA for mean 7.9 years	1	16707	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.32, 2.05]
33 Venous thromboembolism (DVT or PE): oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.25, 8.83]
34 Global cognitive function	4		Mean Difference (Fixed, 95% CI)	Subtotals only
34.1 Transdermal estradiol 0.014 mg (low dose): MMSE scores (baseline MMSE ≤ 90)	1		Mean Difference (Fixed, 95% CI)	-1.21 [-5.05, 2.63]
34.2 Transdermal estradiol 0.014 mg (low dose): MMSE scores (baseline MMSE > 90)	1		Mean Difference (Fixed, 95% CI)	-0.3 [-0.73, 0.13]
34.3 CEE 0.625 mg (mod dose) with or without 2.5 mg MPA for 3 years: MMSE scores	1		Mean Difference (Fixed, 95% CI)	-0.1 [-0.35, 0.15]
34.4 CEE 0.625 mg (mod dose) for mean 5.2 years: MMSE scores	1		Mean Difference (Fixed, 95% CI)	-0.26 [-0.52, 0.00]
34.5 Combined continuous CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 4.2 years: MMSE scores	1		Mean Difference (Fixed, 95% CI)	-0.18 [-0.36, 0.00]
34.6 Oestrogen with or without sequential progesterone vaginal gel	1		Mean Difference (Fixed, 95% CI)	-0.03 [-0.21, 0.15]
35 Probable dementia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 CEE 0.625 mg (mod dose) for 5.2 years	1	2947	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.89, 2.59]

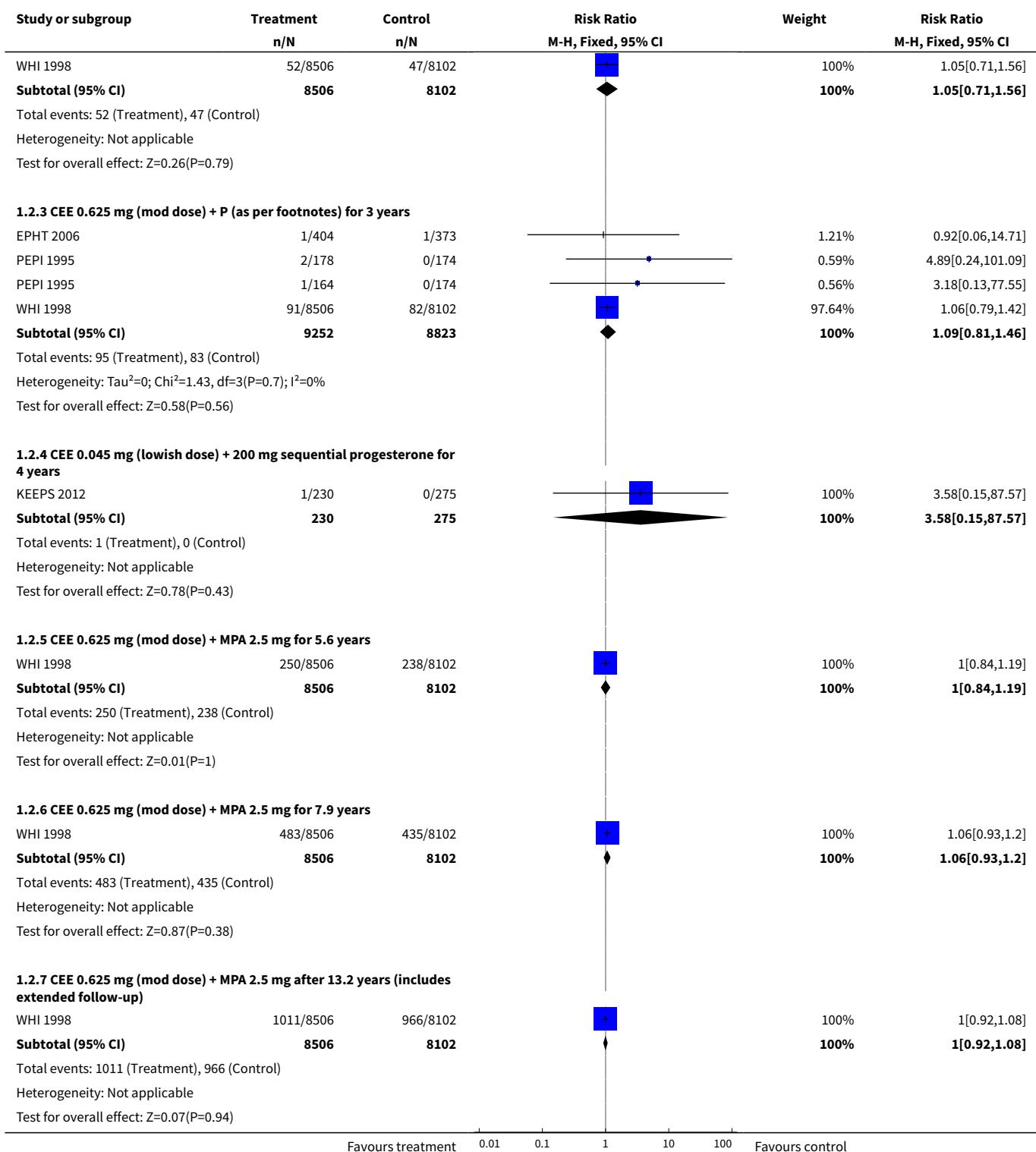
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.2 Combined continuous CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 4.05 years	1	4532	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.16, 3.33]

Analysis 1.1. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 1 Death from any cause: oestrogen-only HT.

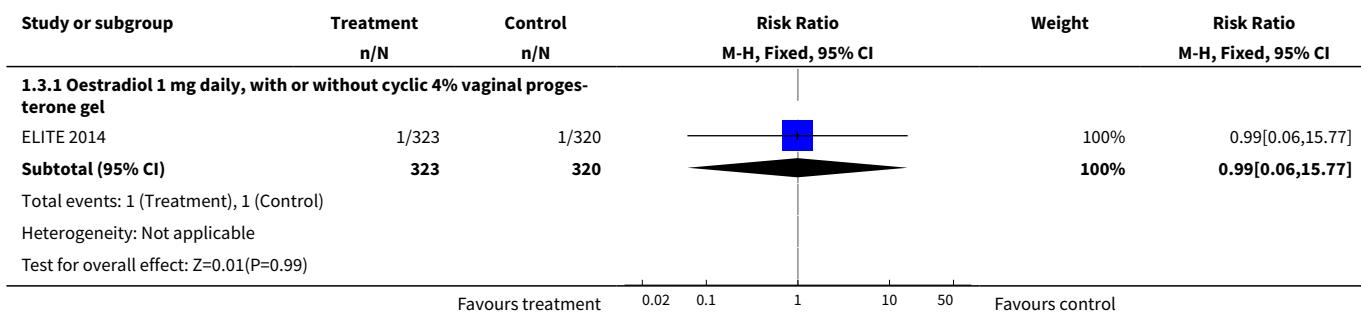


Analysis 1.2. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 2 Death from any cause: combined HT.

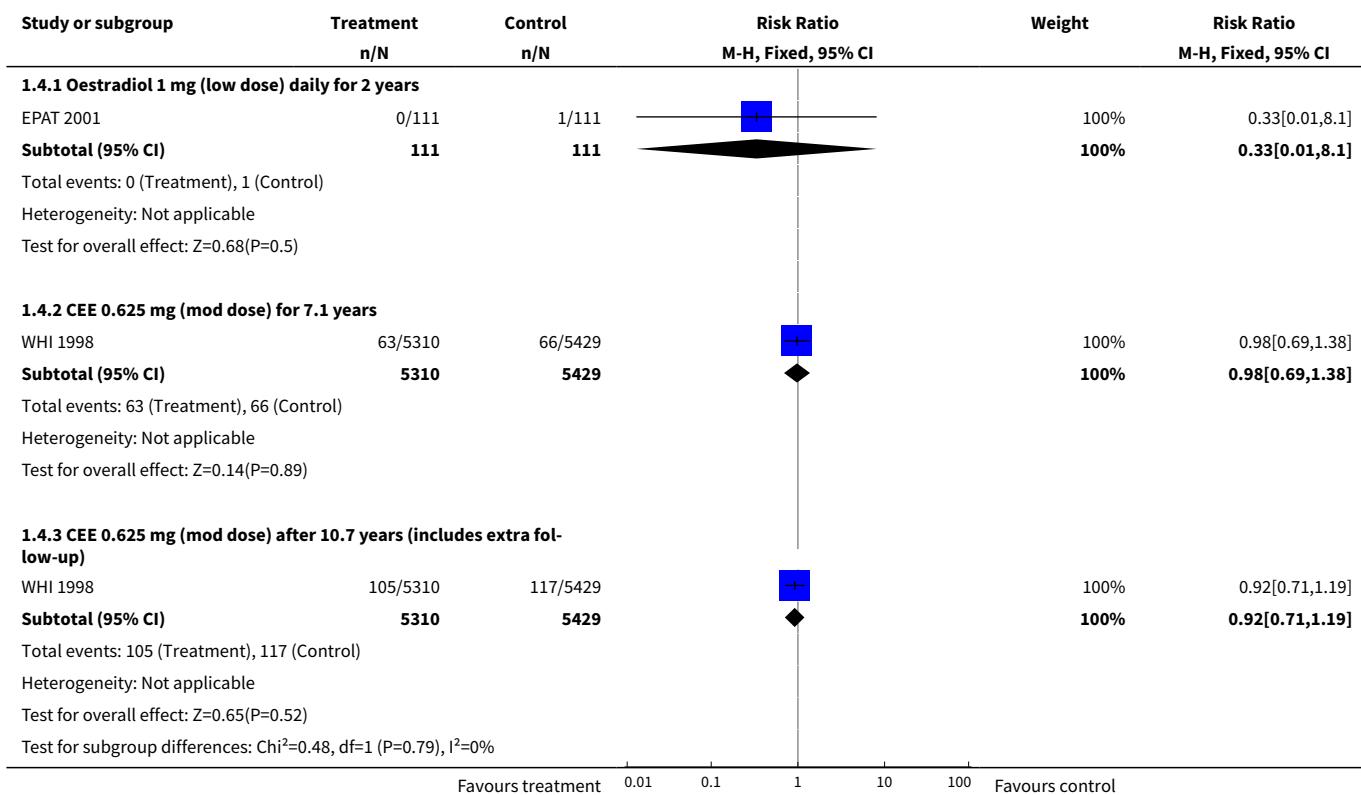




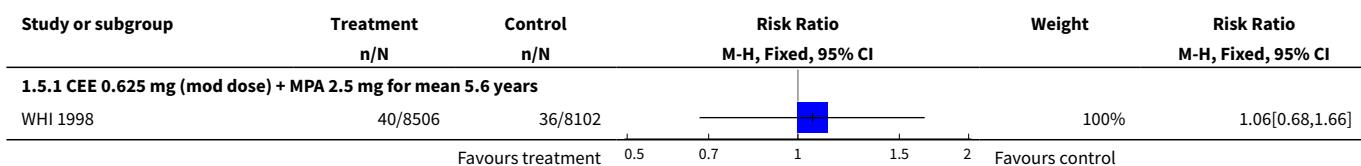
Analysis 1.3. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 3 Death from any cause: oestrogen with or without sequential progesterone vaginal gel.

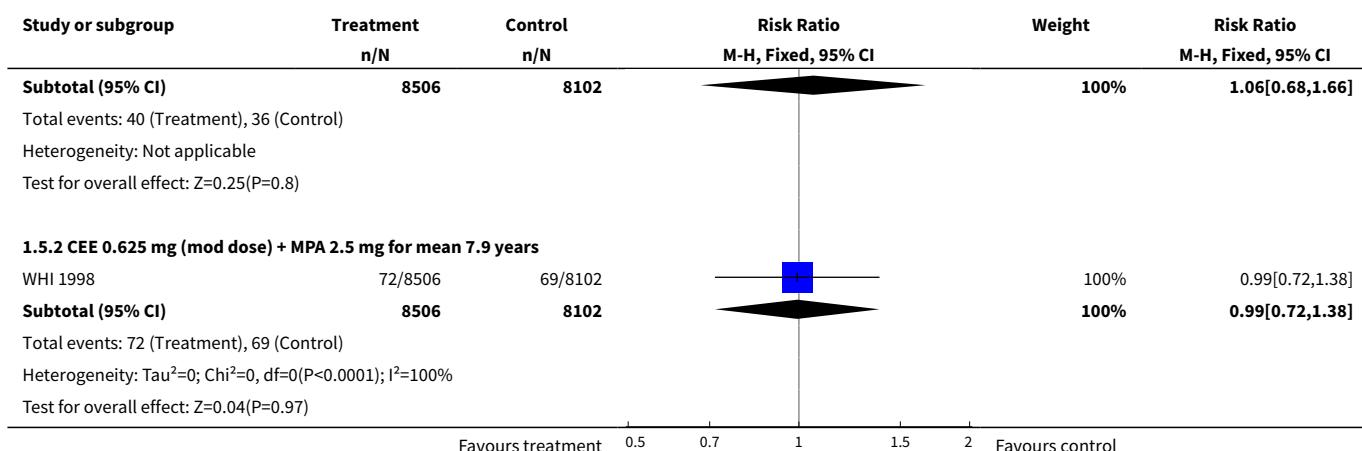


Analysis 1.4. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 4 Death from coronary heart disease: oestrogen-only HT.

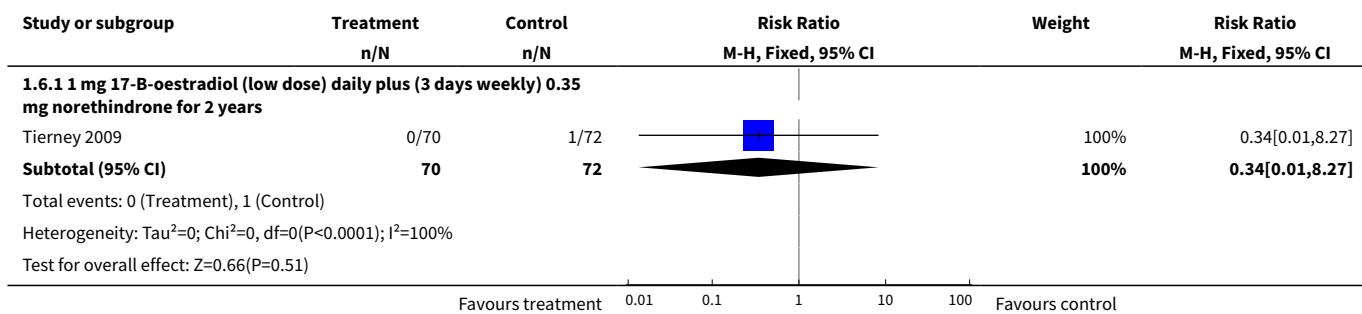


Analysis 1.5. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 5 Death from coronary heart disease: combined continuous HT.

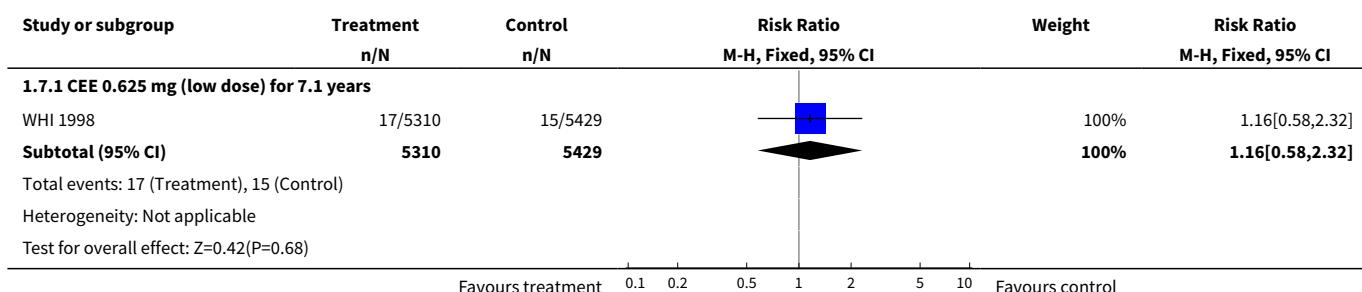


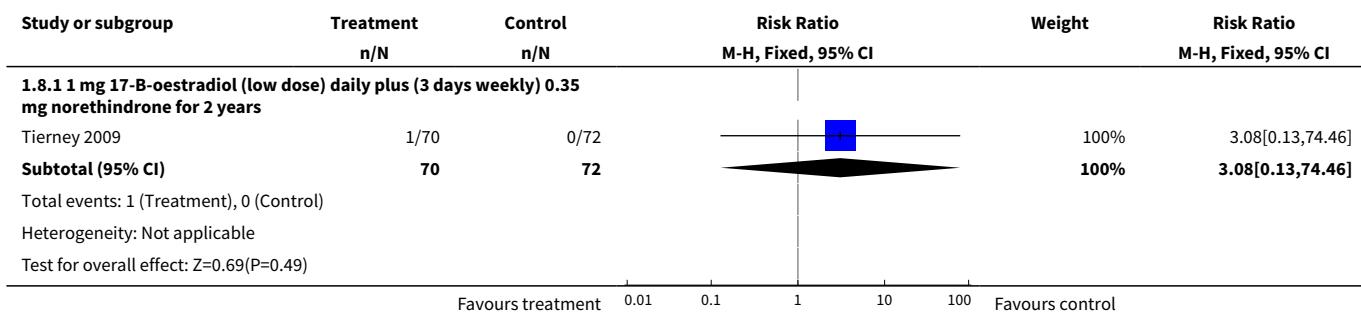
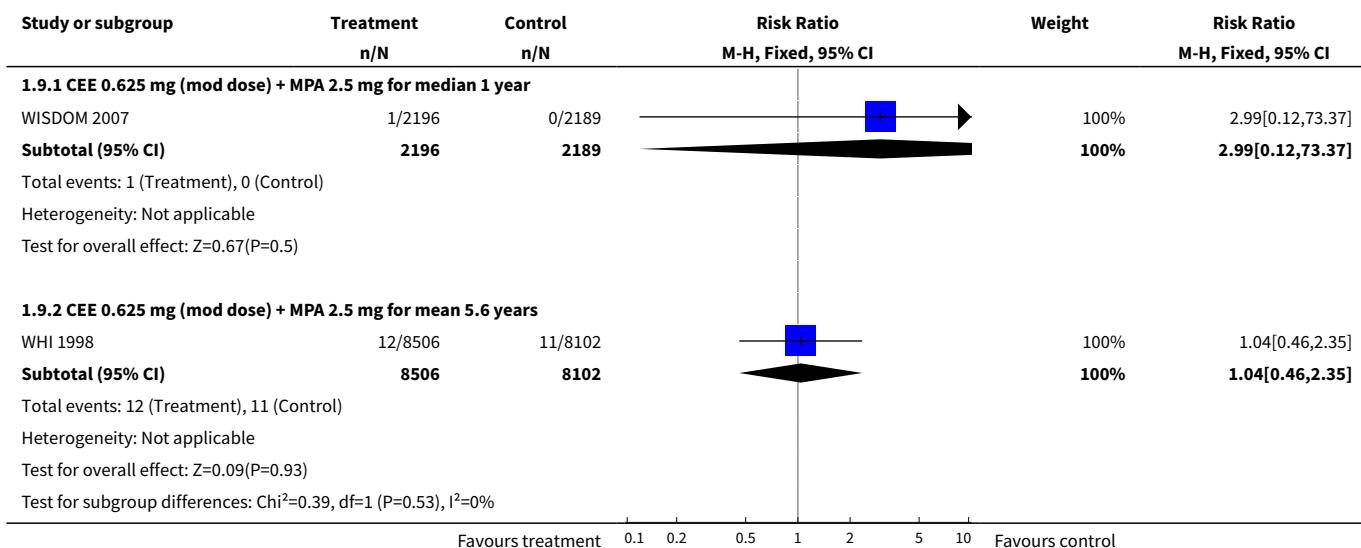
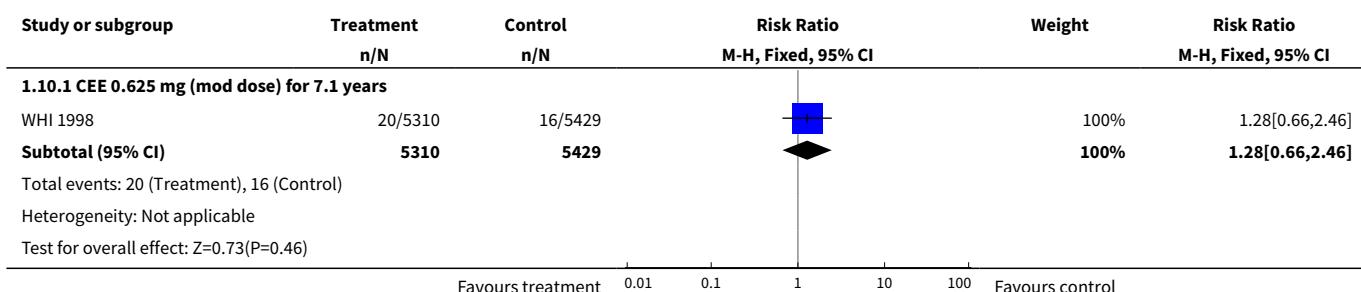


Analysis 1.6. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 6 Death from coronary heart disease: combined sequential HT.

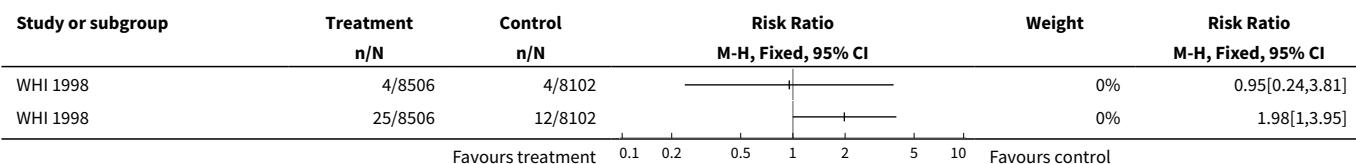


Analysis 1.7. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 7 Death from stroke: oestrogen-only HT.

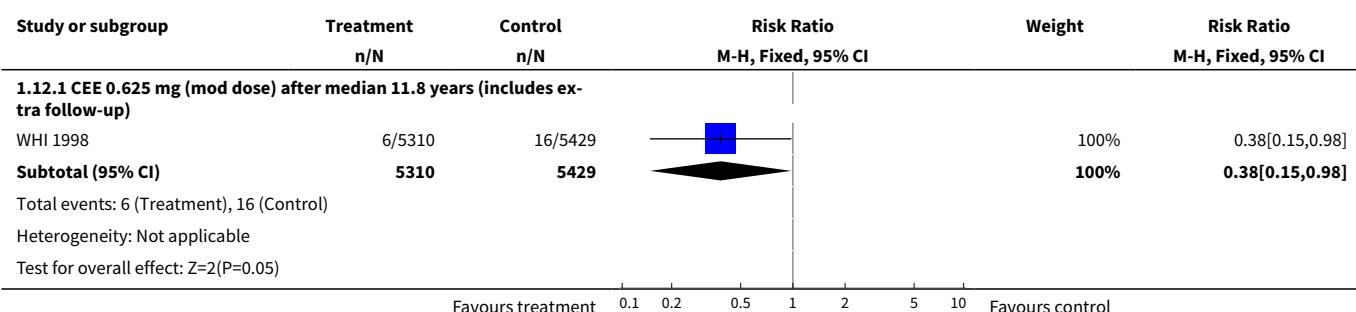


Analysis 1.8. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 8 Death from stroke: combined sequential HT.

Analysis 1.9. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 9 Death from stroke: combined continuous HT.

Analysis 1.10. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 10 Death from colorectal cancer: oestrogen-only HT.


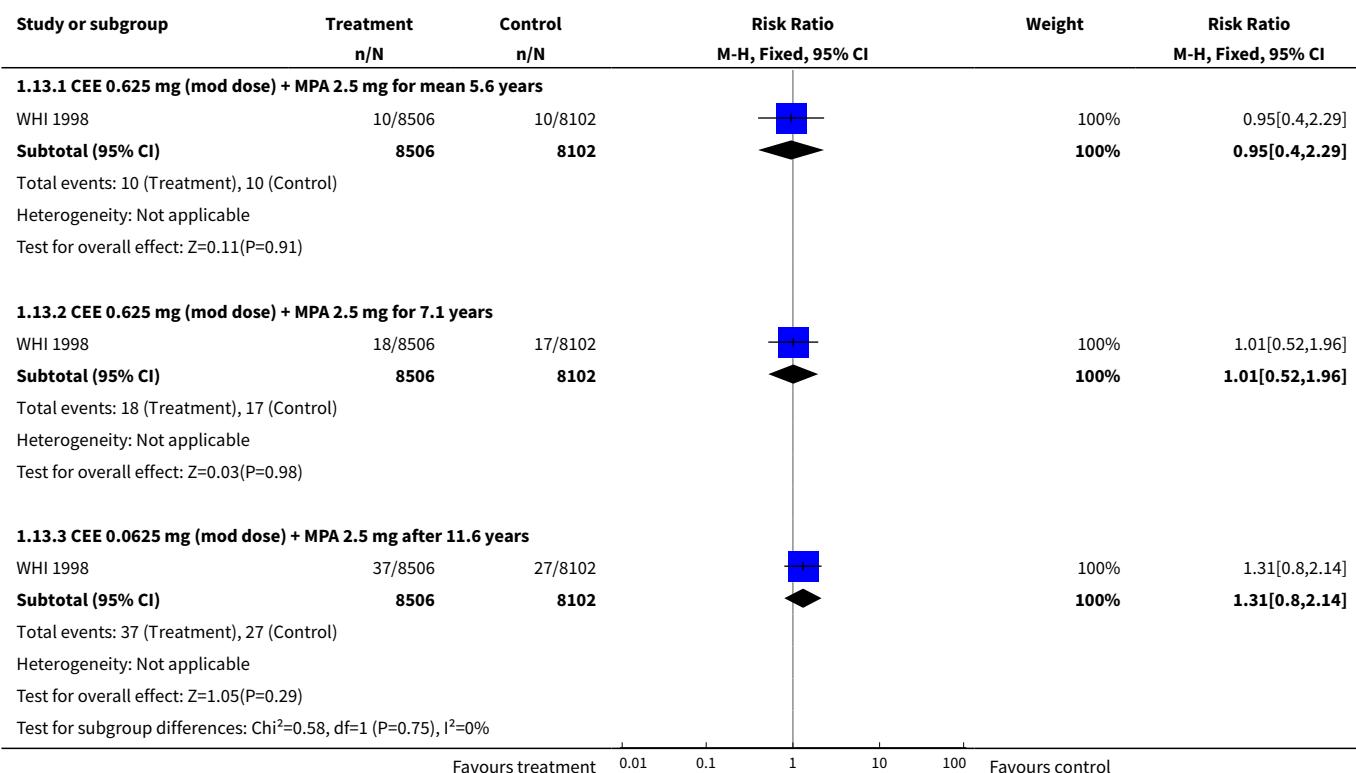
Analysis 1.11. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 11 Death from breast cancer: combined continuous HT.



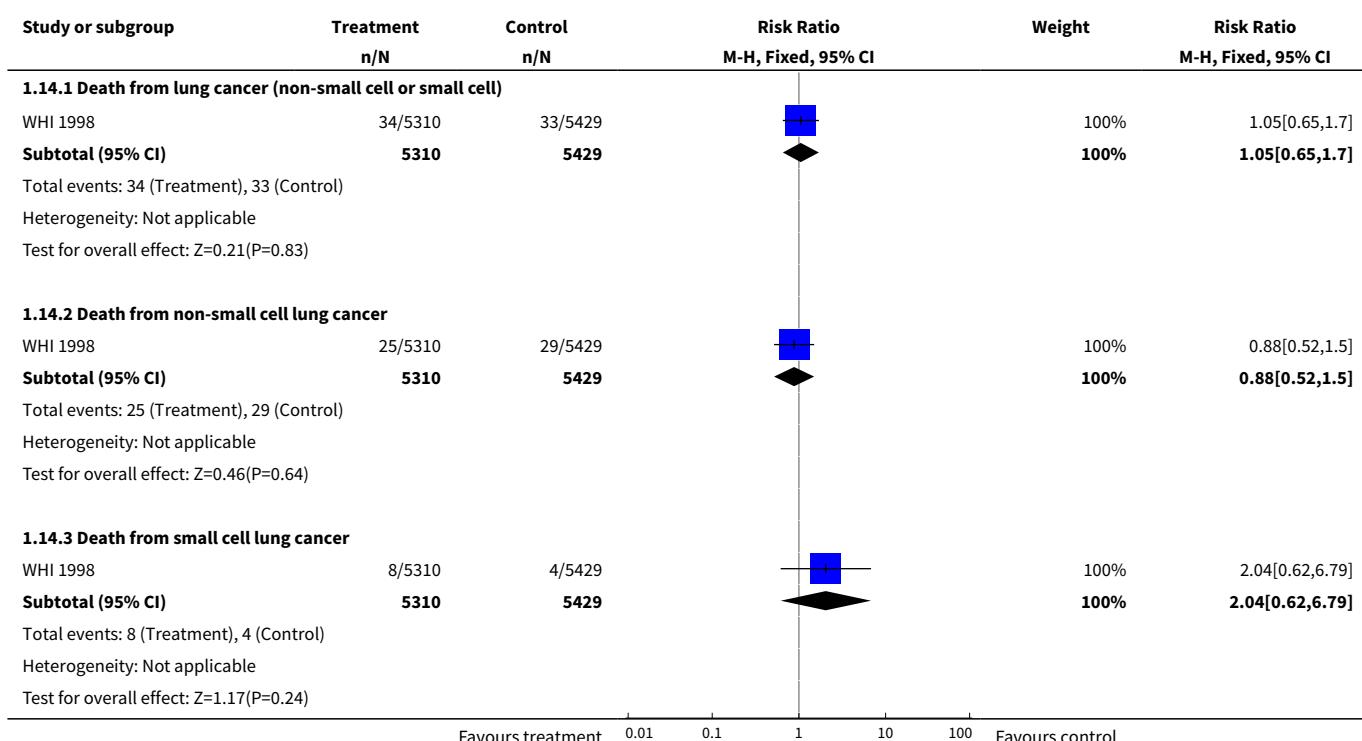
Analysis 1.12. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 12 Death from breast cancer: oestrogen-only HT.



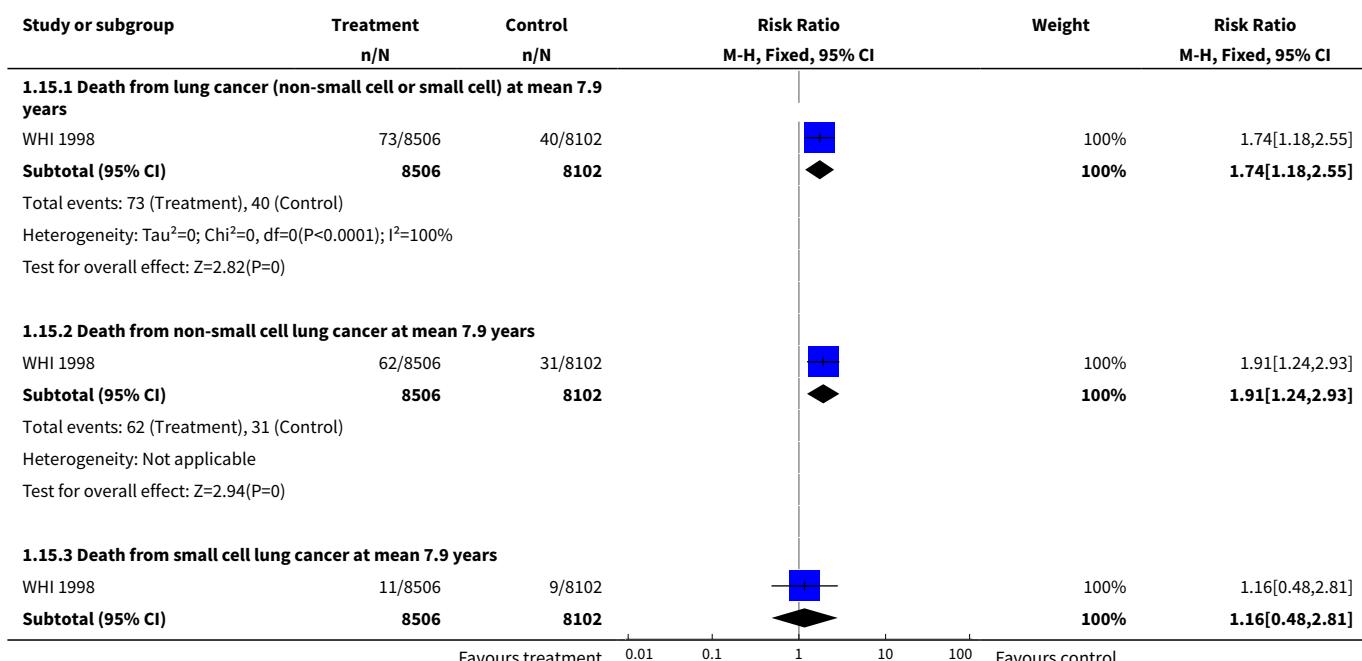
Analysis 1.13. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 13 Death from colorectal cancer: combined continuous HT.

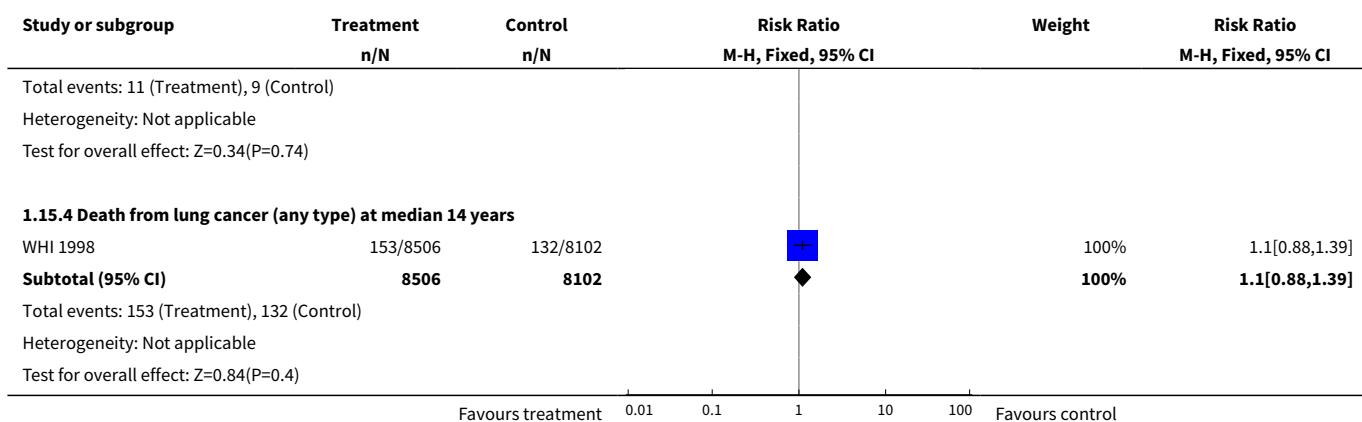


Analysis 1.14. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 14 Death from lung cancer: oestrogen-only HT (moderate dose).

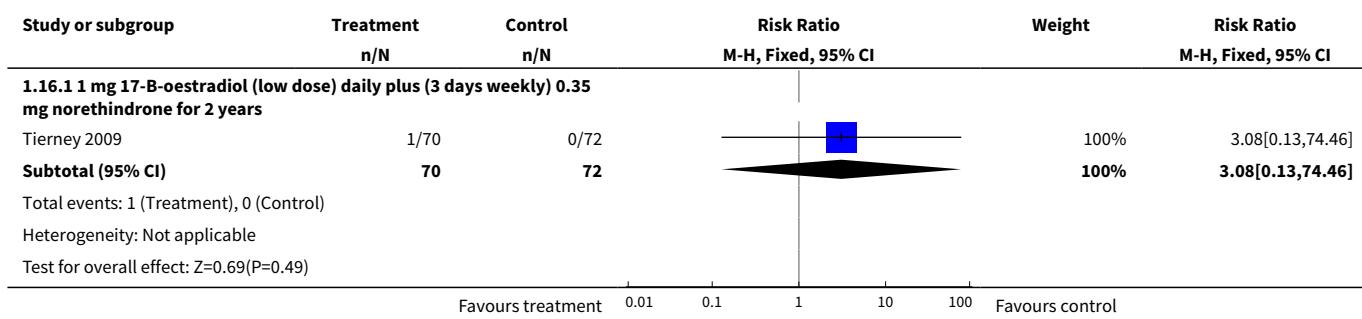


Analysis 1.15. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 15 Death from lung cancer: combined continuous HT (moderate dose).

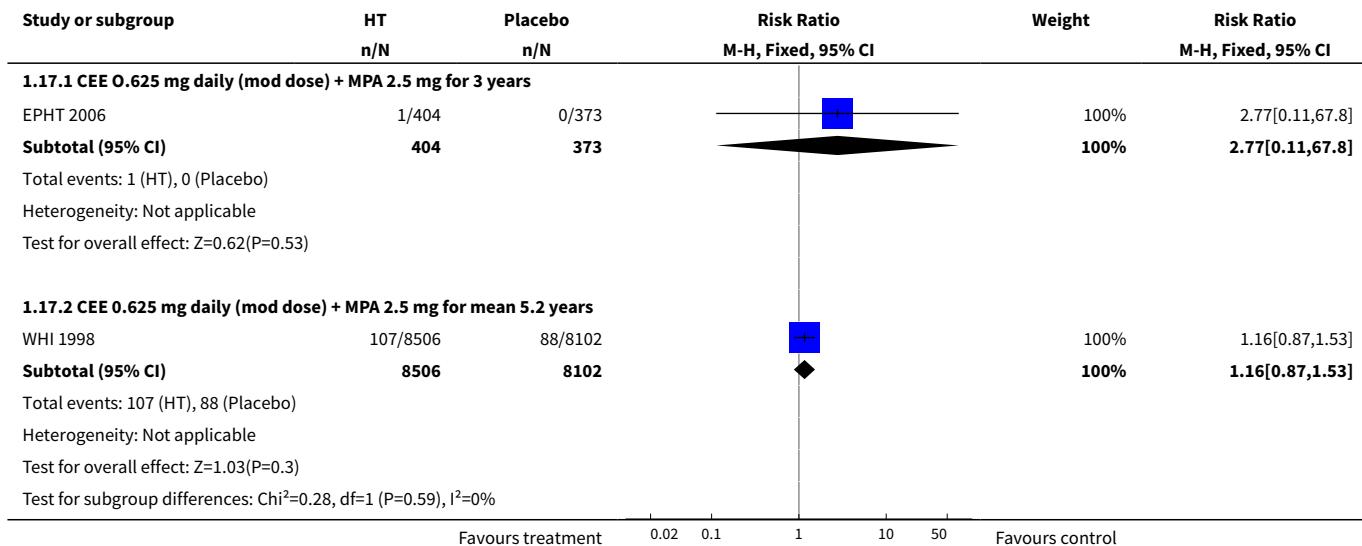




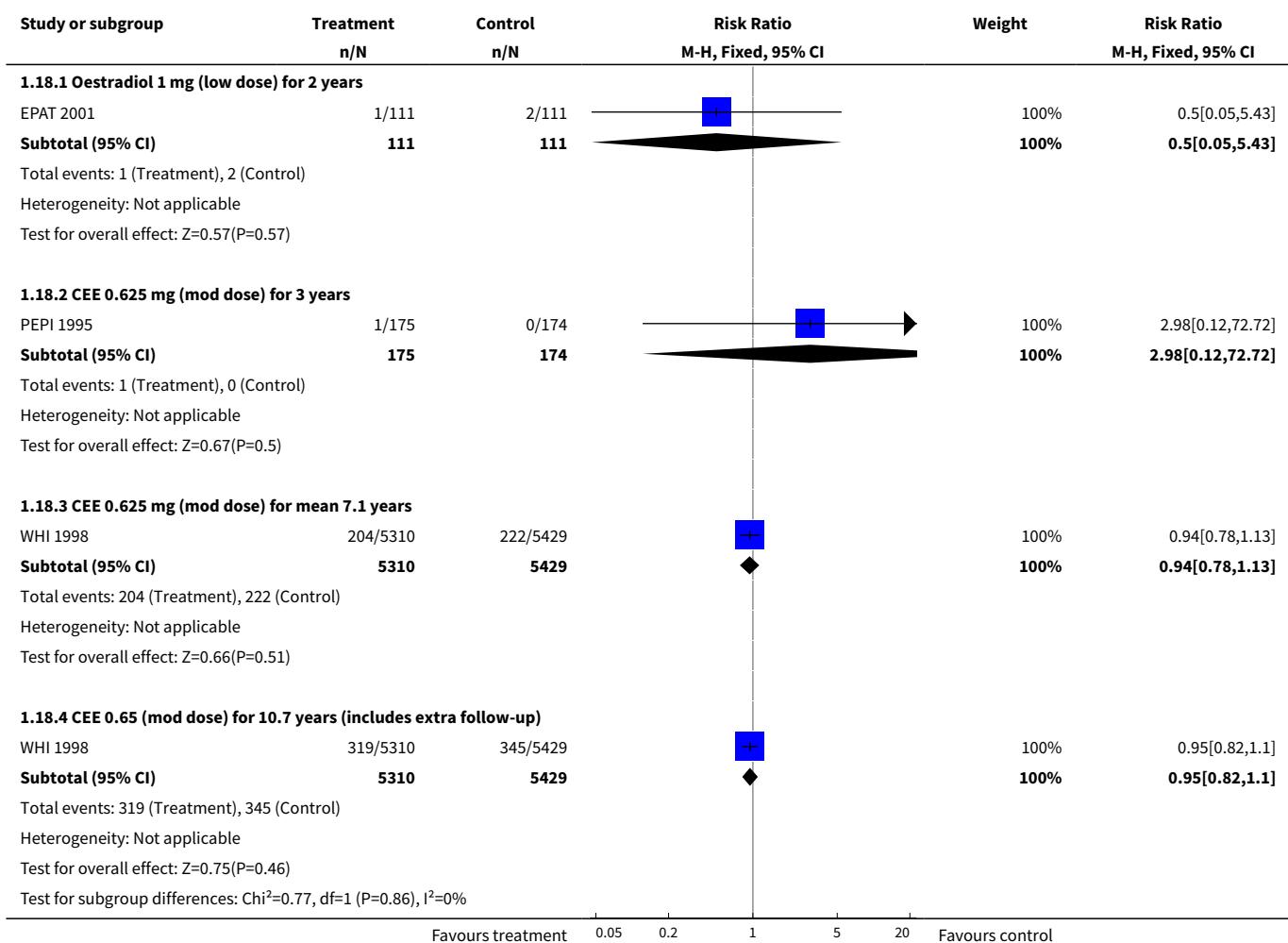
Analysis 1.16. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 16 Death from lung cancer: combined sequential HT (low dose oestrogen).



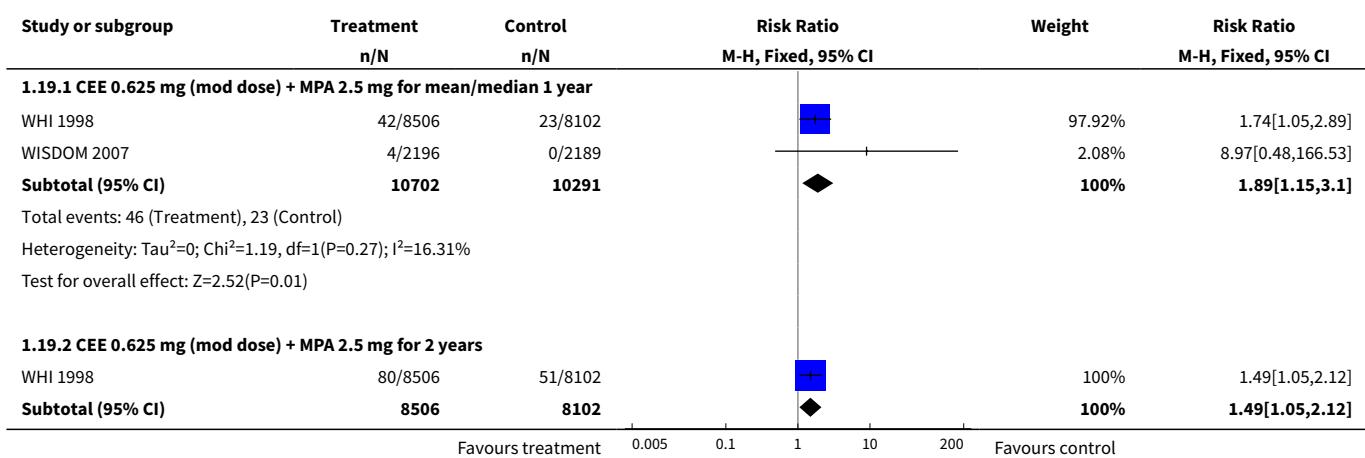
Analysis 1.17. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 17 Death from any cancer: combined continuous HT.

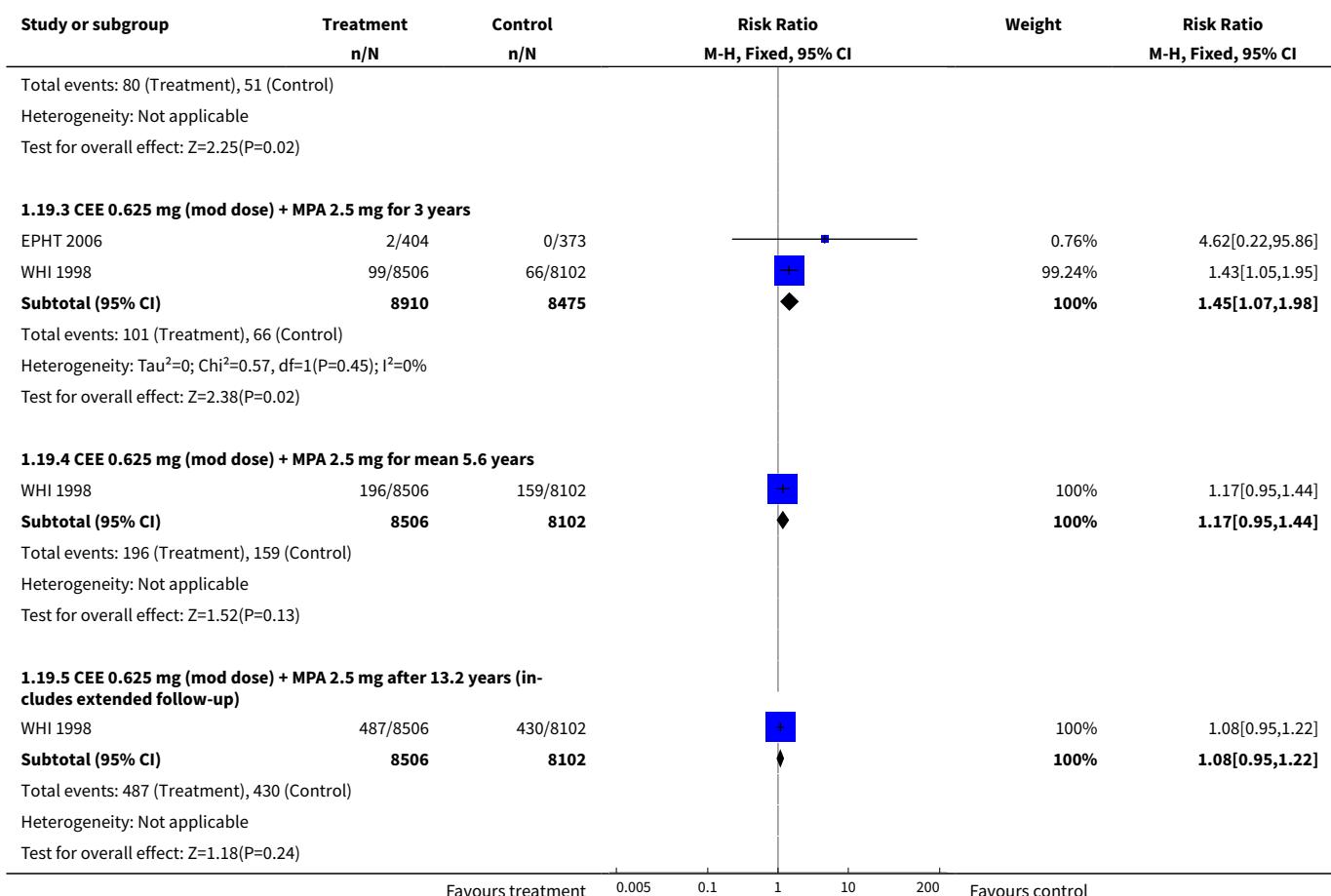


Analysis 1.18. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 18 Coronary events (MI or cardiac death): oestrogen-only HT.

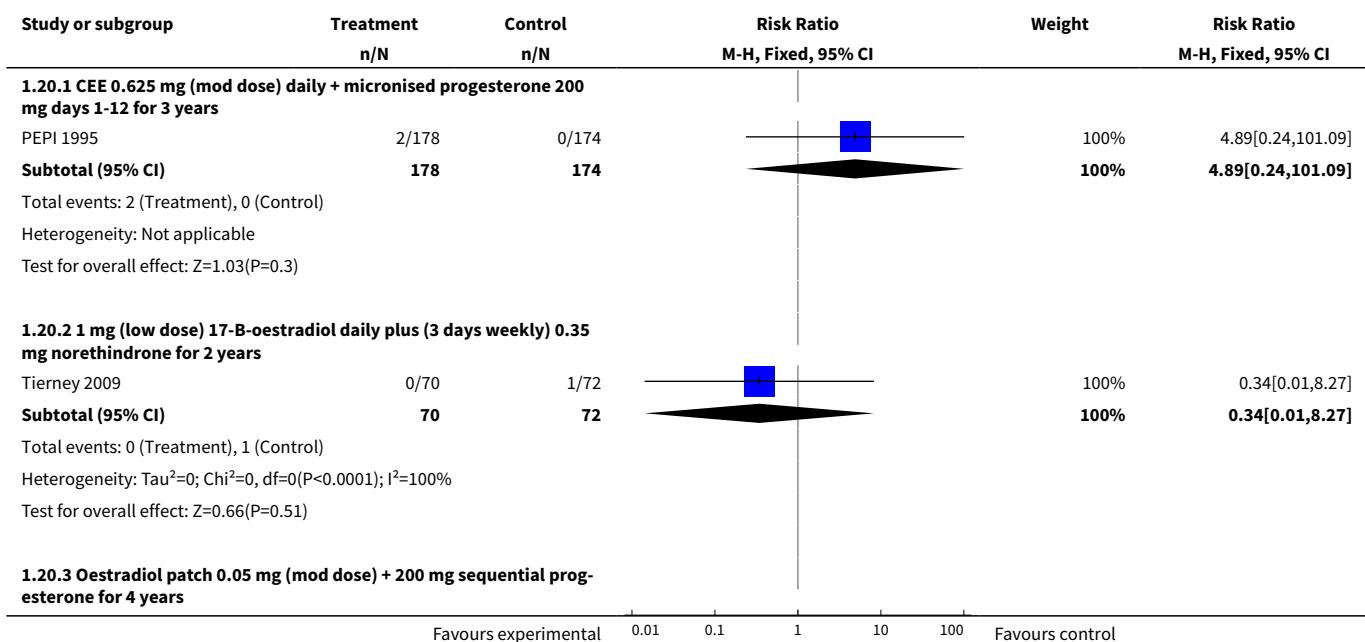


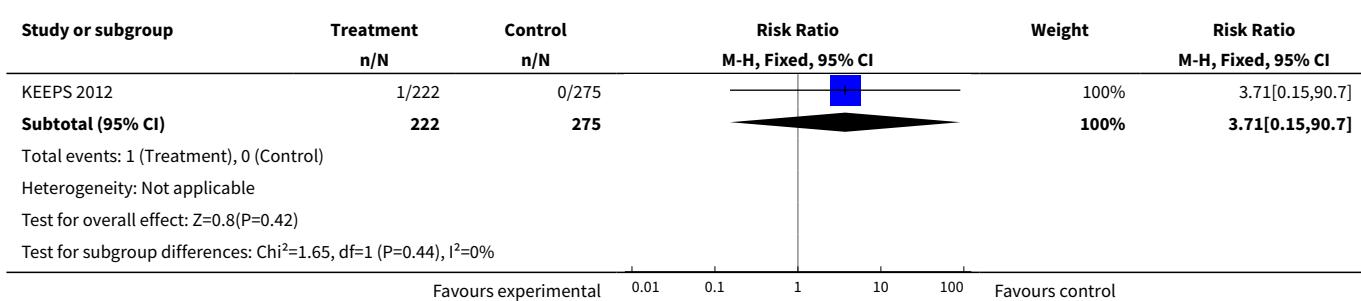
Analysis 1.19. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 19 Coronary events (MI or cardiac death): combined continuous HT.



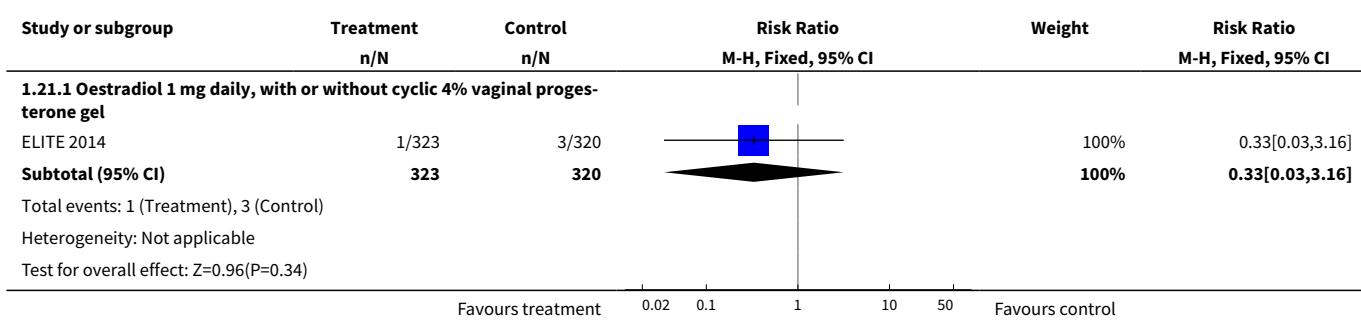


Analysis 1.20. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 20 Coronary events (MI or cardiac death): combined sequential HT.

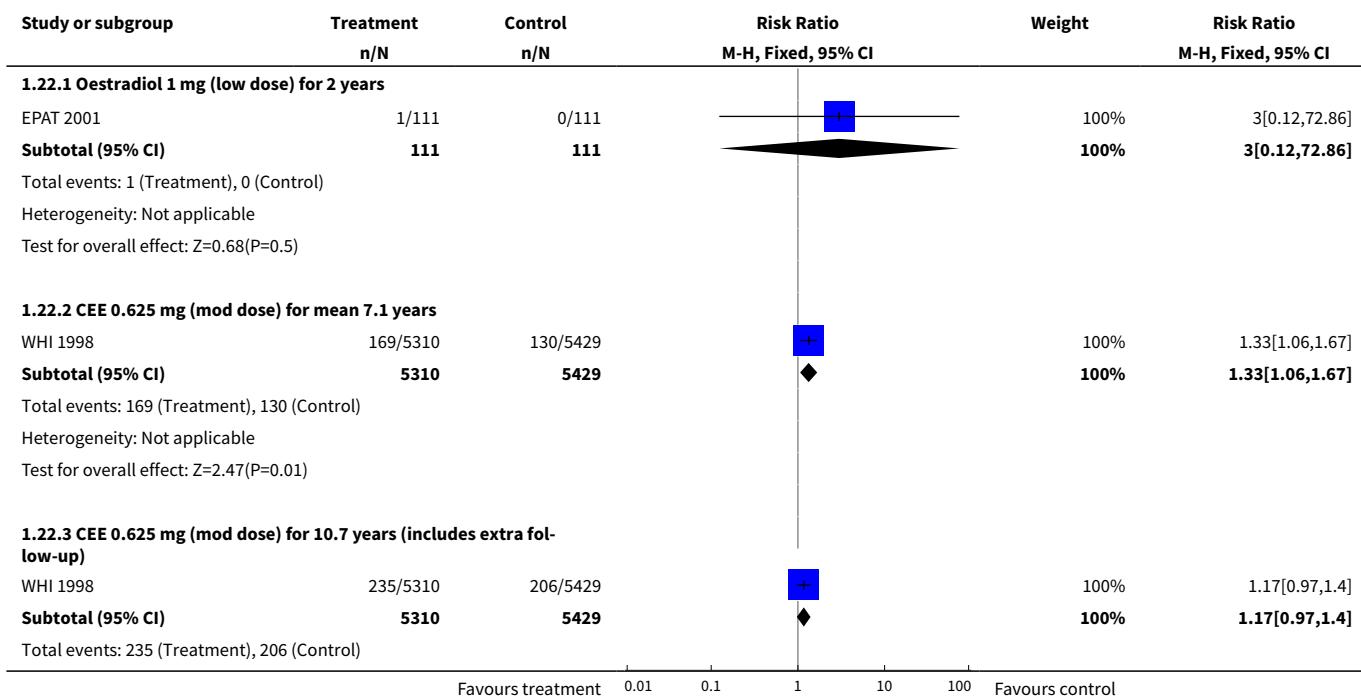


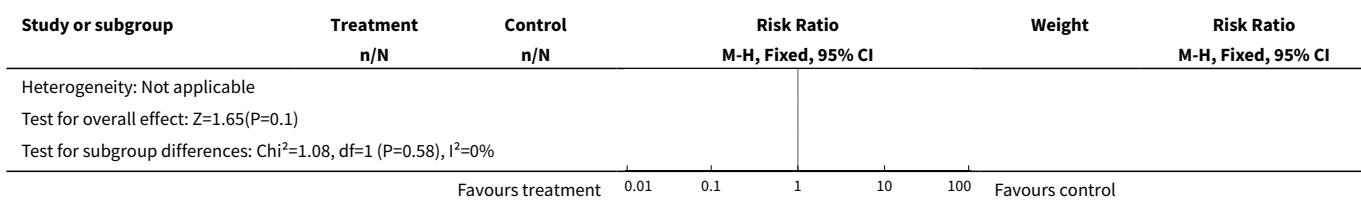


Analysis 1.21. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 21 Coronary events (MI or cardiac death): oestrogen with or without sequential progesterone vaginal gel.

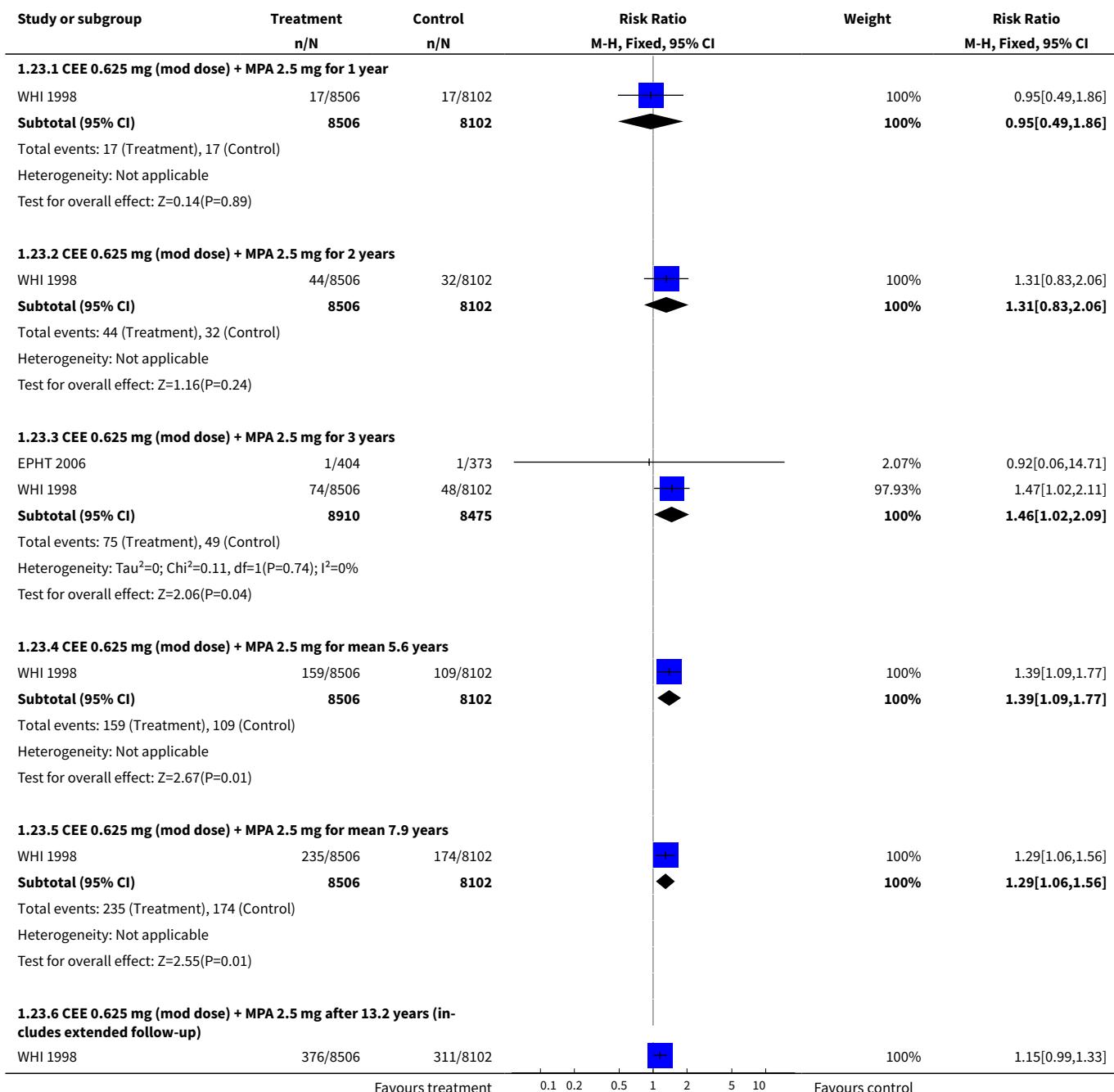


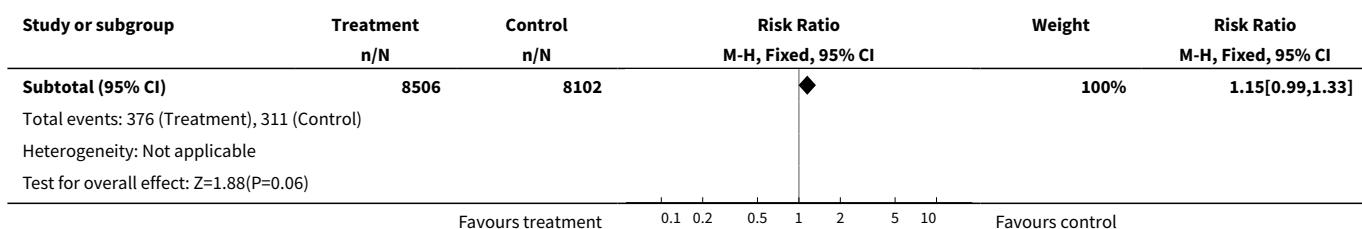
Analysis 1.22. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 22 Stroke: unopposed oestrogen.



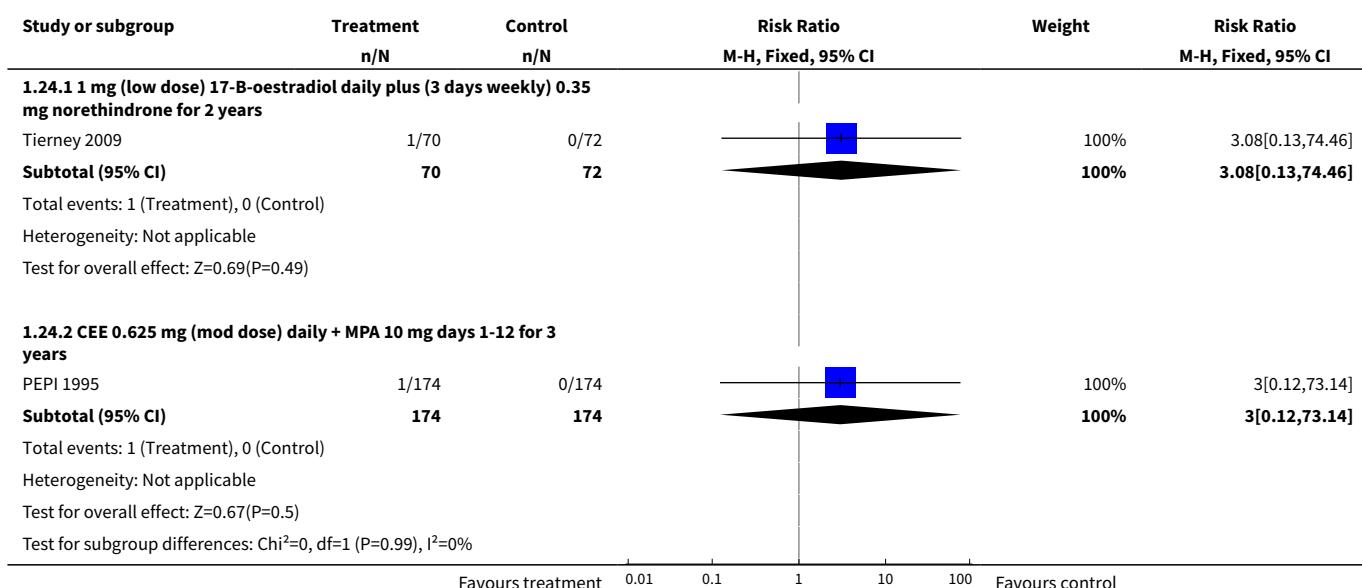


Analysis 1.23. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 23 Stroke: combined continuous HT.

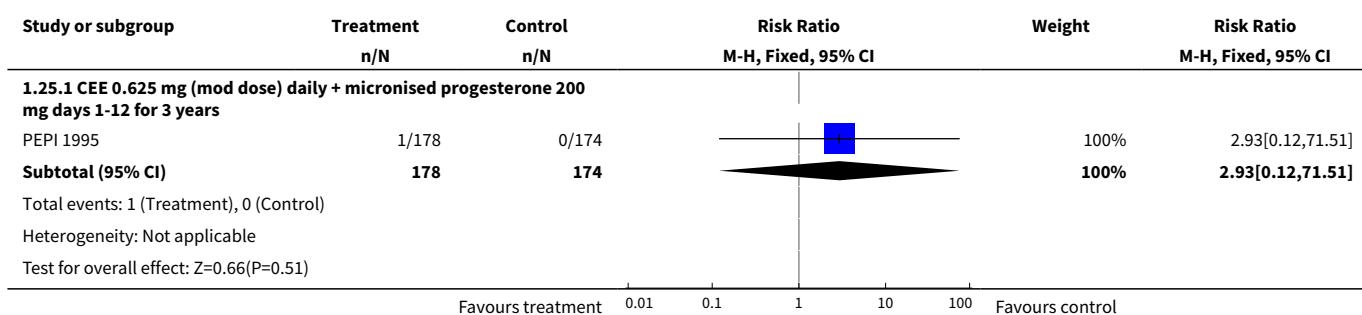




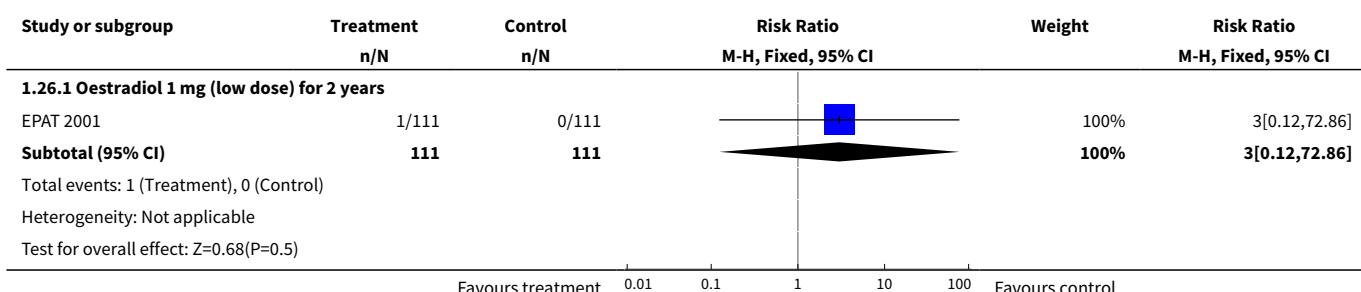
Analysis 1.24. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 24 Stroke: combined sequential HT.



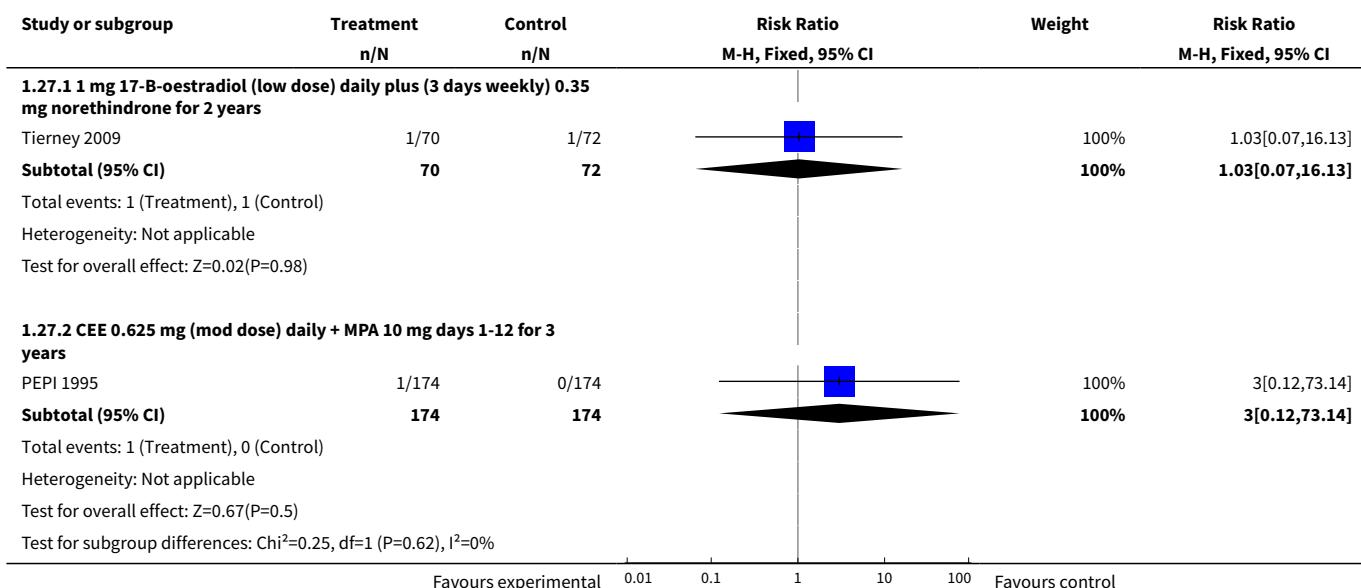
Analysis 1.25. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 25 Stroke: combined sequential HT.



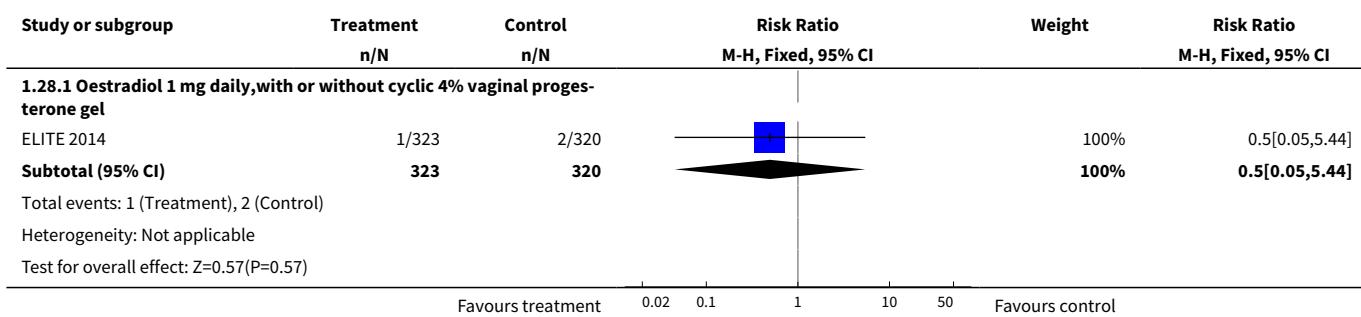
Analysis 1.26. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 26 Transient ischaemic attack: oestrogen-only HT.



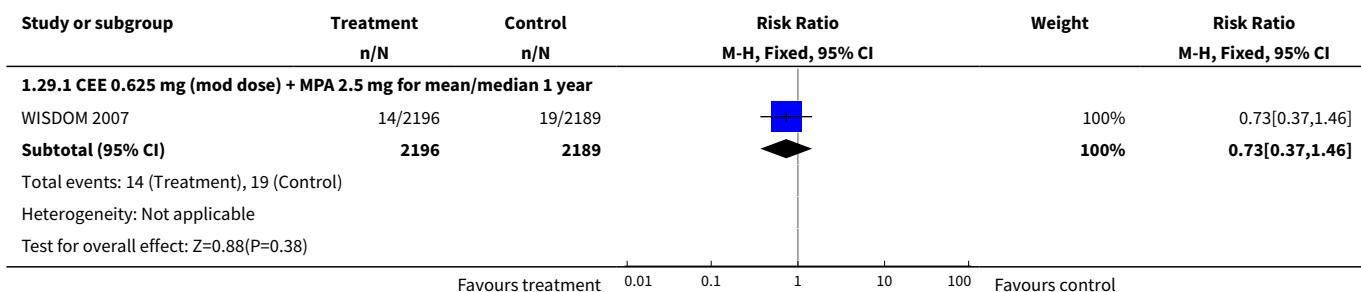
Analysis 1.27. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 27 Transient ischaemic attack: combined sequential HT.



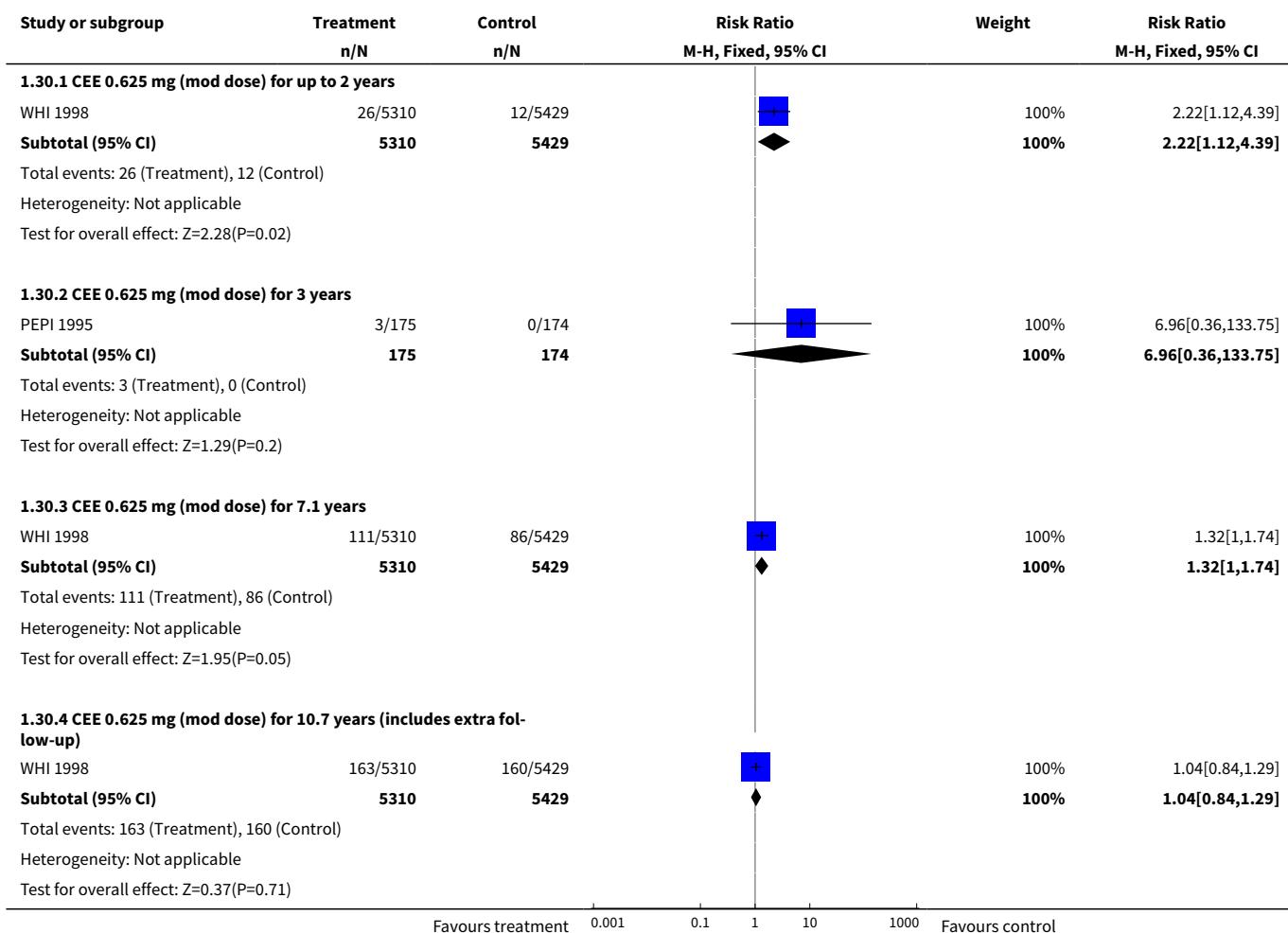
Analysis 1.28. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 28 Transient ischaemic attack: oestrogen with or without sequential progesterone vaginal gel.



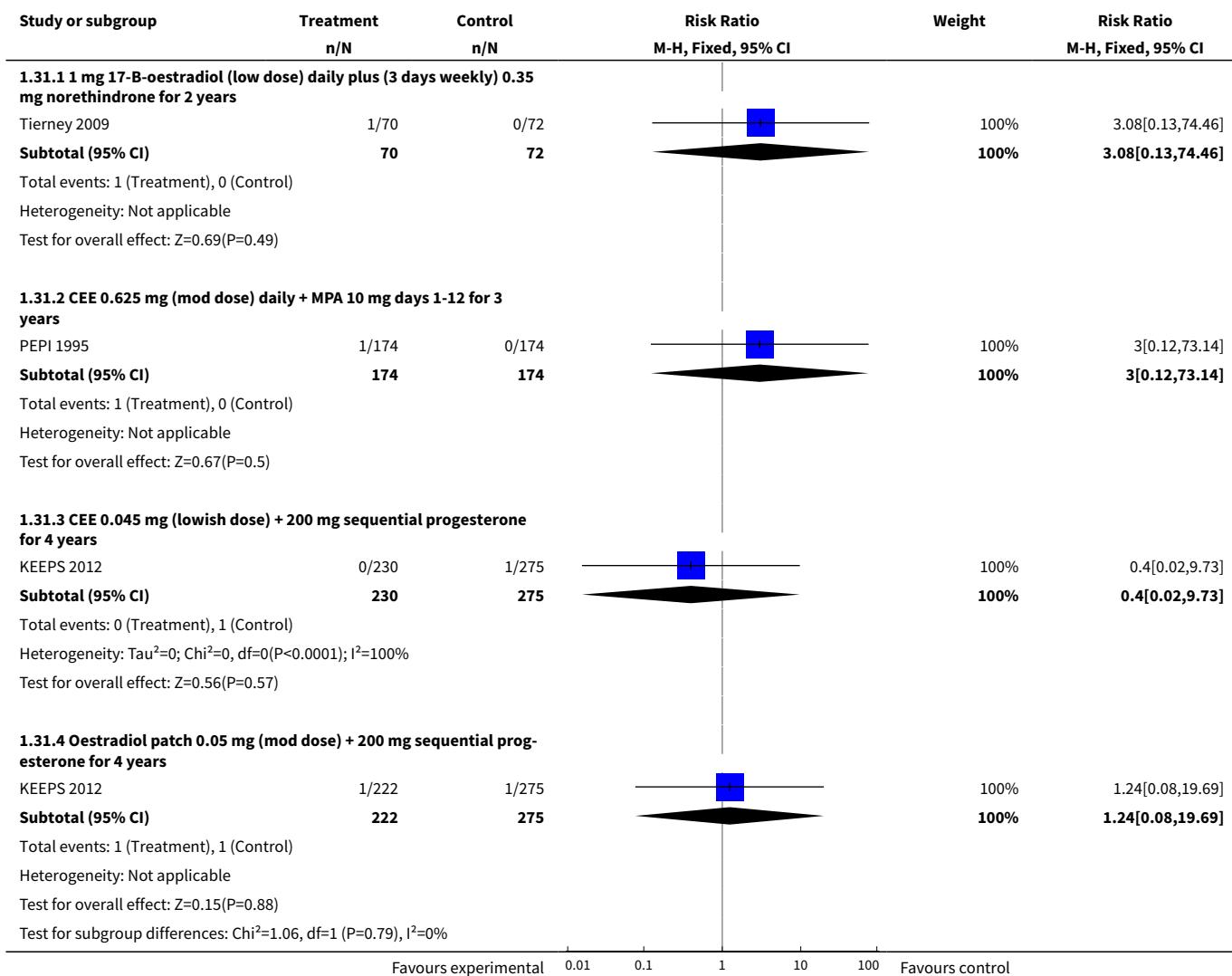
Analysis 1.29. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 29 Stroke or transient ischaemic attack.



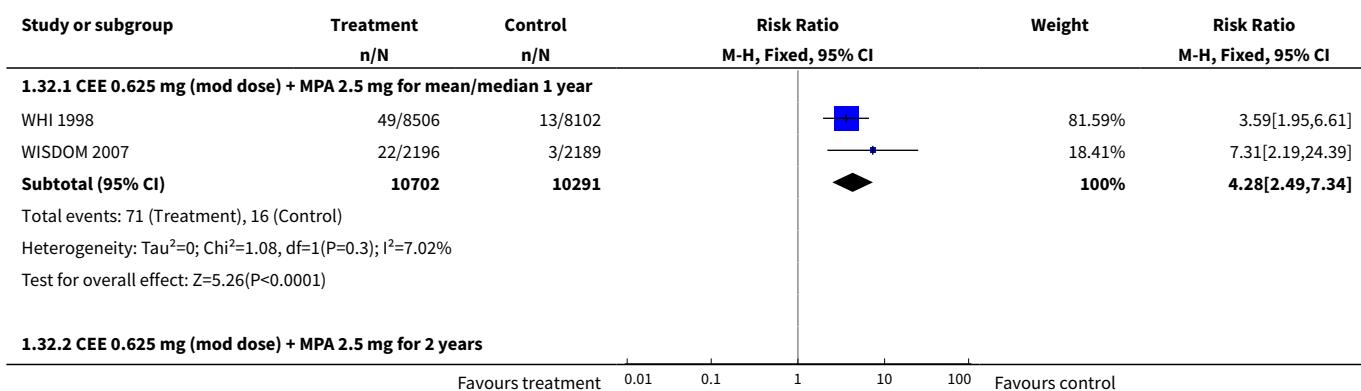
Analysis 1.30. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 30 Venous thromboembolism (DVT or PE): oestrogen-only HT.

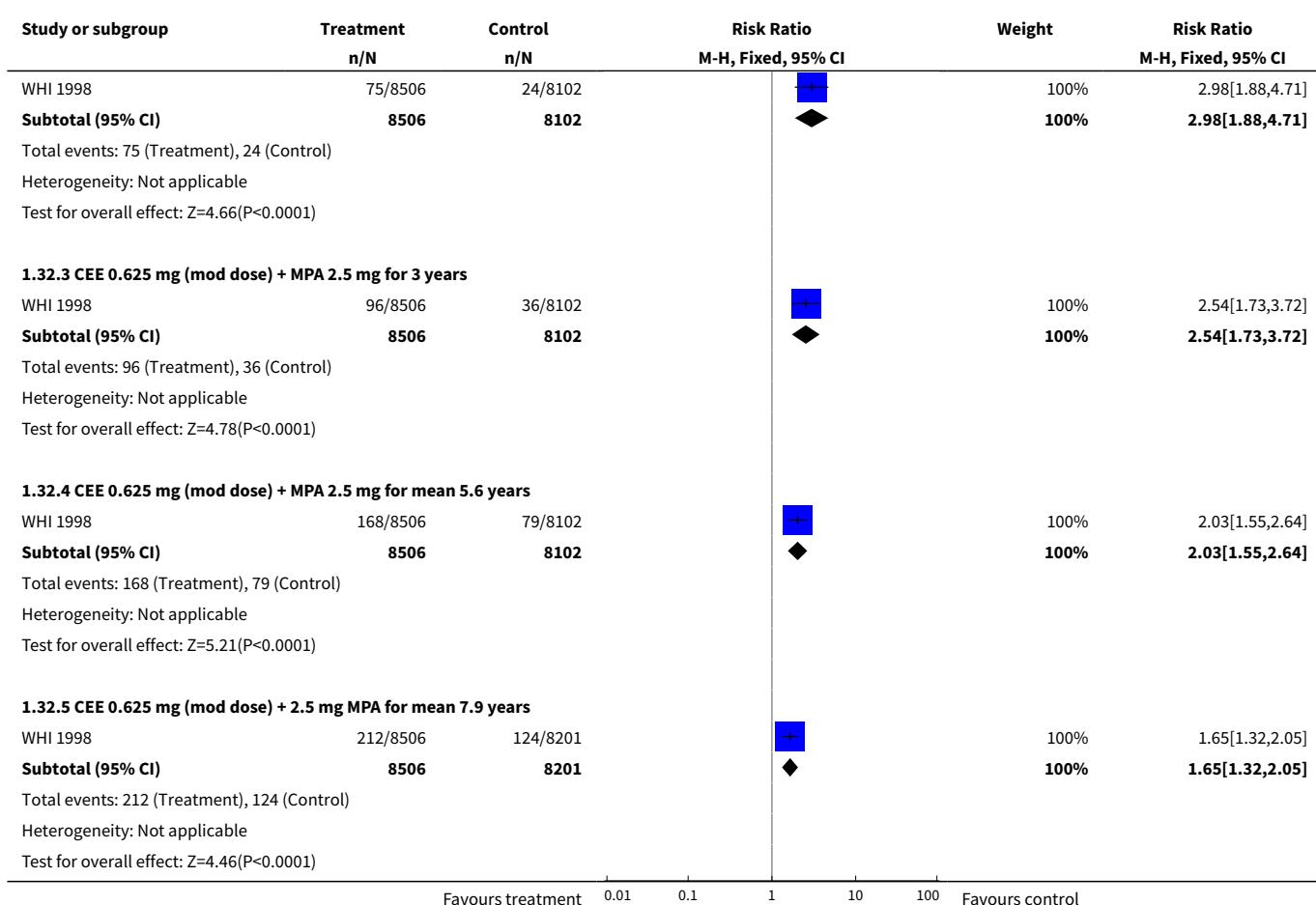


Analysis 1.31. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 31 Venous thromboembolism (DVT or PE): combined sequential HT.

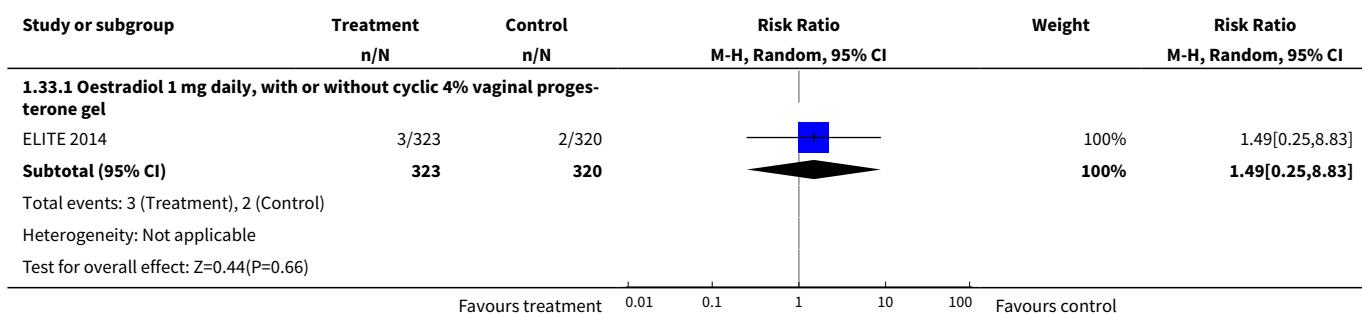


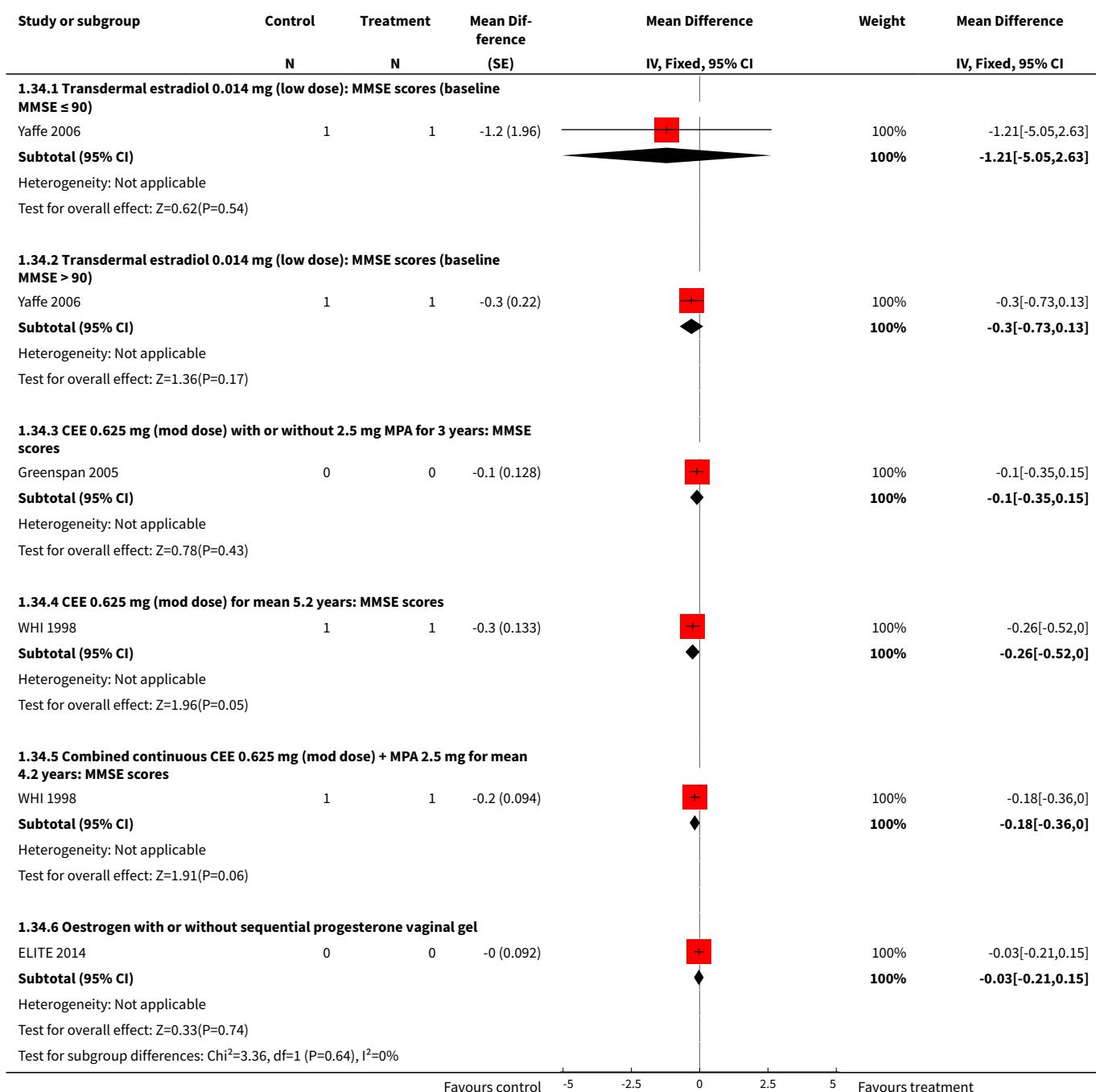
Analysis 1.32. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 32 Venous thromboembolism (DVT or PE): combined continuous HT.

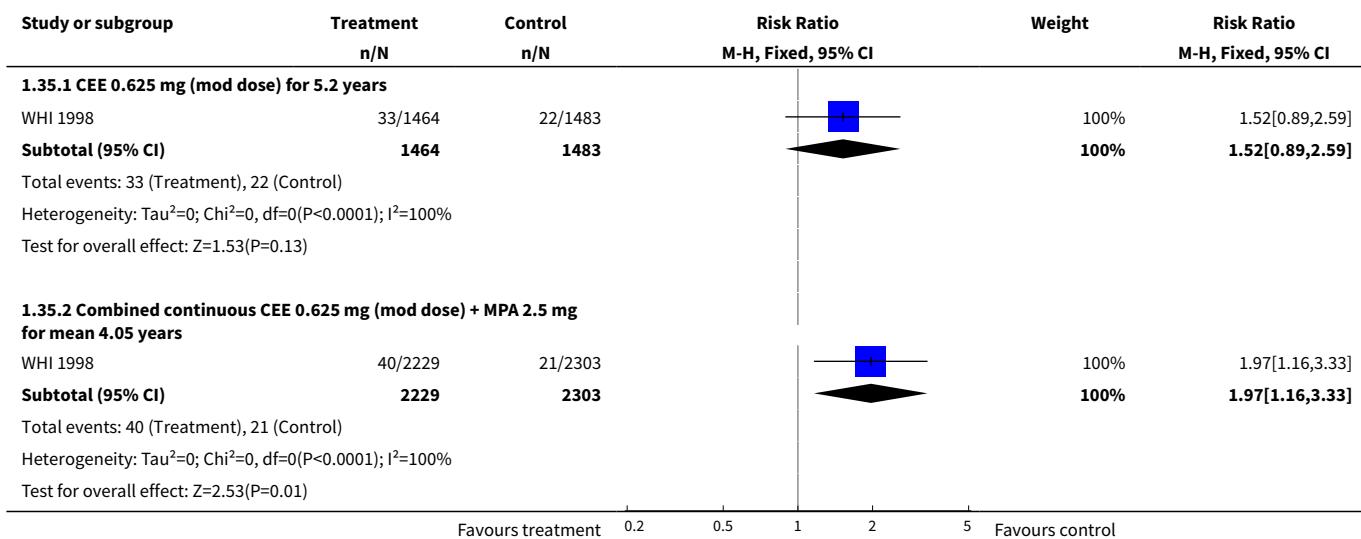




Analysis 1.33. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 33 Venous thromboembolism (DVT or PE): oestrogen with or without sequential progesterone vaginal gel.



Analysis 1.34. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 34 Global cognitive function.


Analysis 1.35. Comparison 1 Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome 35 Probable dementia.

Comparison 2. Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from any cause: oestrogen-only HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CEE 0.625 mg (mod dose) daily for 3 years (2.8-3.2)	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.53, 3.22]
1.2 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.51, 1.27]
2 Death from any cause: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.67]
3 Death from any cause: combined continuous HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2.8-3.2 years	2	297	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.28, 2.62]
3.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.34]
3.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-7 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.90, 1.44]

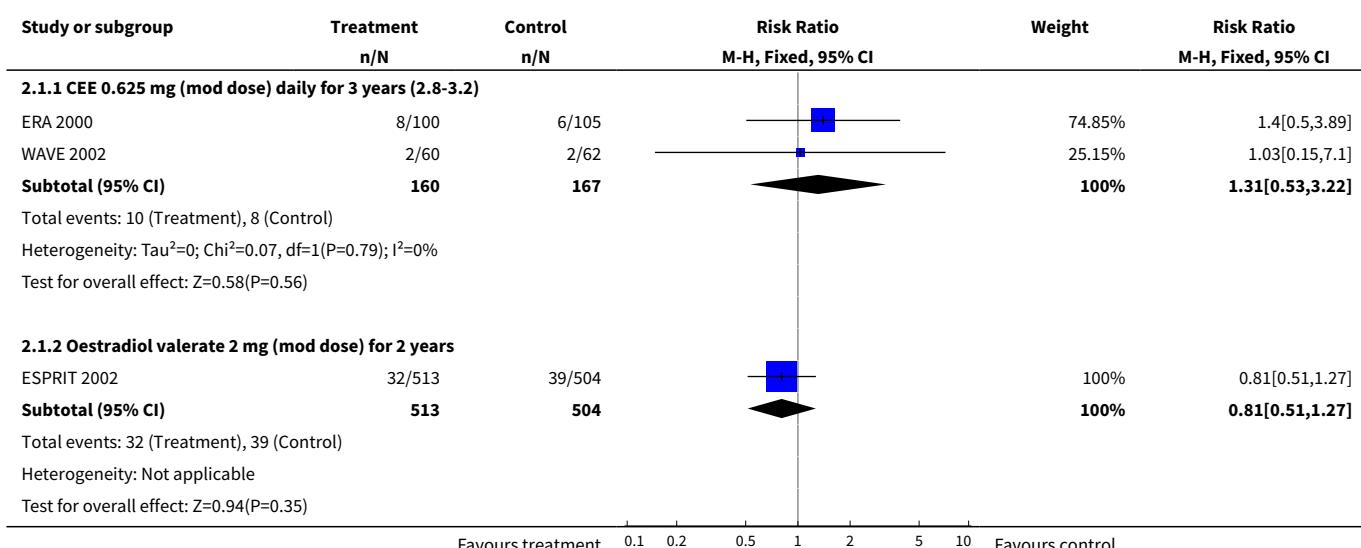
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Death from coronary heart disease: oestrogen-only HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 CEE 0.625 mg (mod dose) daily for 2.8-3.2 years	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.36, 4.77]
4.2 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.40, 1.18]
5 Death from CHD: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.37, 1.81]
6 Death from CHD: combined continuous HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 CEE 0.625 mg (mod dose) daily + MPA 2.5 mg for 1 year	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.73, 3.29]
6.2 CEE 0.625 mg (mod dose) daily + MPA 2.5 mg for 2 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.90, 2.51]
6.3 CEE 0.625 mg (mod dose) daily + MPA 2.5 mg for 3 years (2.8-3.2)	3	3060	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.88, 1.90]
6.4 CEE 0.625 mg (mod dose) daily + MPA 2.5 mg for 4+ years (median 4.1)	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.67]
6.5 CEE 0.625 mg (mod dose) daily + MPA 2.5 mg for 4-6.8 years	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.39]
7 Coronary event (MI or cardiac death): oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.39]
8 Death from stroke: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.95, 8.93]
9 Death from cancer: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 CEE 0.625 mg daily (mod dose) + MPA 2.5 mg for 4+ years (median 4.1)	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
9.2 CEE 0.625 mg daily (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.86, 2.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Coronary event (MI or cardiac death): oestrogen-only HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 CEE 0.625 (mod dose) daily for 2.8-3.2 years	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.40]
11 Coronary event: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.57, 1.65]
12 Coronary event (MI or cardiac death): combined continuous HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 1 year	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.00, 2.25]
12.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.91, 1.58]
12.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years (2.8-3.2)	3	3060	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.33]
12.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for median 4.1 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.19]
12.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.29]
13 Stroke (first or recurrent): oestrogen-only HT or combined sequential	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Oestradiol 1 mg daily (low dose) (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.51]
14 Stroke (first or recurrent): oestrogen-only HT (mod dose)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 CEE 0.625 mg (mod dose) daily for 2.8 years	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.12, 3.98]
14.2 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.60, 4.47]
15 Stroke (first or recurrent): combined continuous HT (mod dose oestrogen)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Continuous oestradiol 2 mg (mod dose) + norethisterone acetate 1 mg for 1.3 years	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.82]
15.2 CEE 0.625 mg (mod dose) + MPA for 2.8 years	1	88	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [0.26, 105.85]

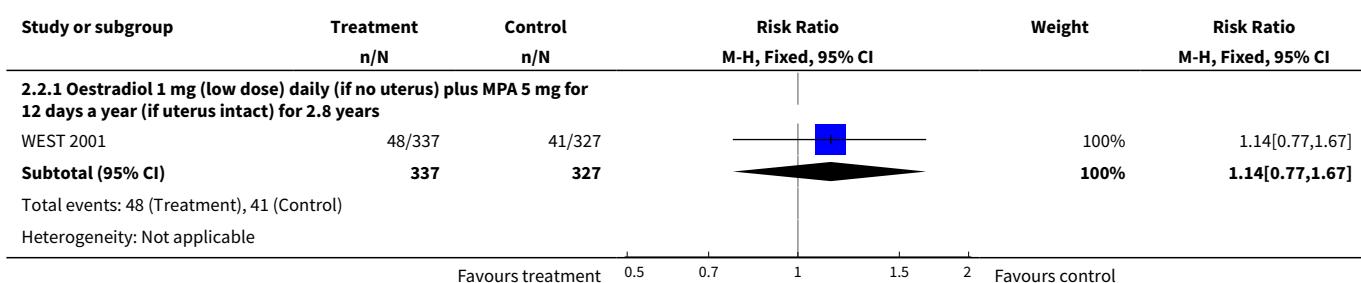
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for median 4.1 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.68]
15.4 CEE 0.625 mg (mod dose) + MPA for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.71, 1.57]
16 Transient ischaemic attack: oestrogen-only HT (mod dose)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.36]
17 Transient ischaemic attack: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.70, 1.94]
18 Transient ischaemic attack: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.23]
18.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.49, 1.84]
19 Stroke or transient ischaemic attack: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 CEE 0.625 mg (mod dose) daily for 3.2 years	1	205	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.28, 2.78]
20 Stroke or transient ischaemic attack: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3.2 years	1	209	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.34, 3.03]
21 VTE (first or recurrent PE or DVT): oestrogen-only HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.33, 4.55]
21.2 CEE 0.625 mg (mod dose) daily for 2.8-3.2 years	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.44, 6.17]
22 VTE (first or recurrent PE or DVT): combined continuous HT	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 1 year	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [1.06, 9.96]

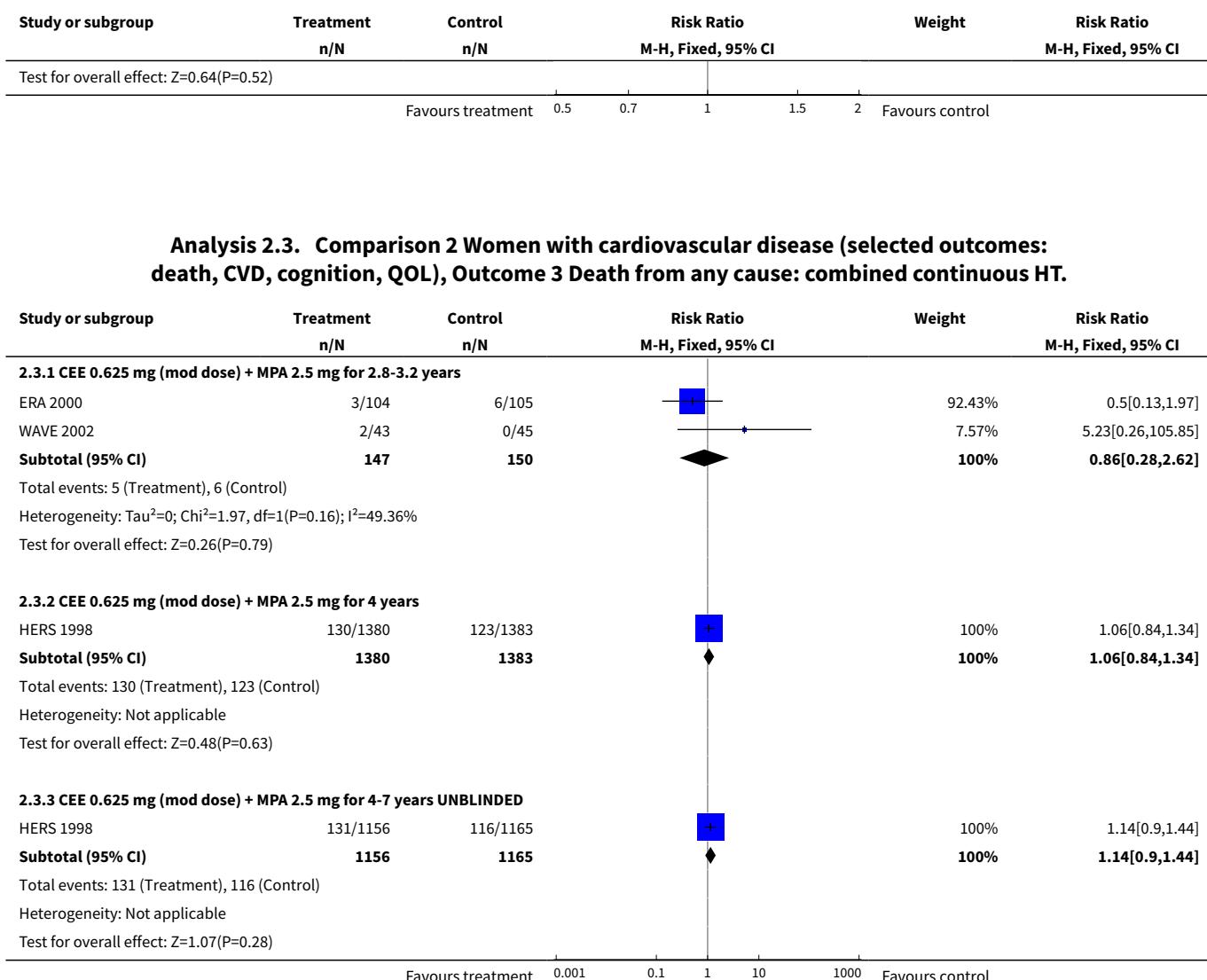
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Continuous oestradiol 2 mg (mod dose) + norethisterone acetate 1 mg for 1.3 years	1	140	Risk Ratio (M-H, Fixed, 95% CI)	6.80 [0.86, 53.85]
22.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [1.42, 8.66]
22.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years (2.8-3.2)	3	3060	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [1.50, 6.04]
22.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for median 4.1 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [1.39, 4.94]
22.6 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-7 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.98]

Analysis 2.1. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 1 Death from any cause: oestrogen-only HT.

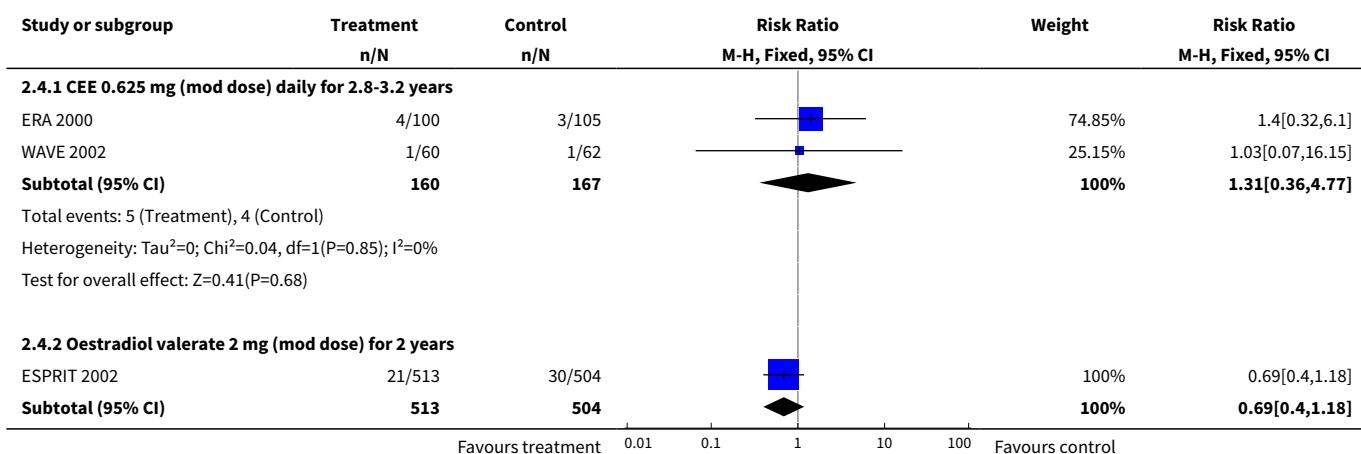


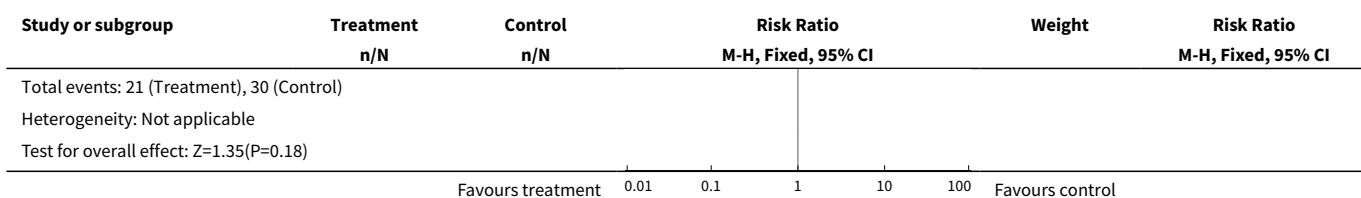
Analysis 2.2. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 2 Death from any cause: oestrogen-only or combined sequential HT.



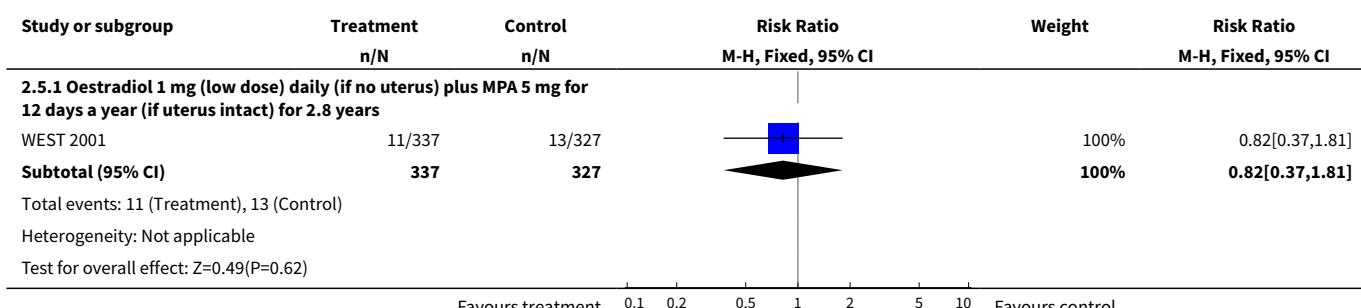


Analysis 2.4. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 4 Death from coronary heart disease: oestrogen-only HT.

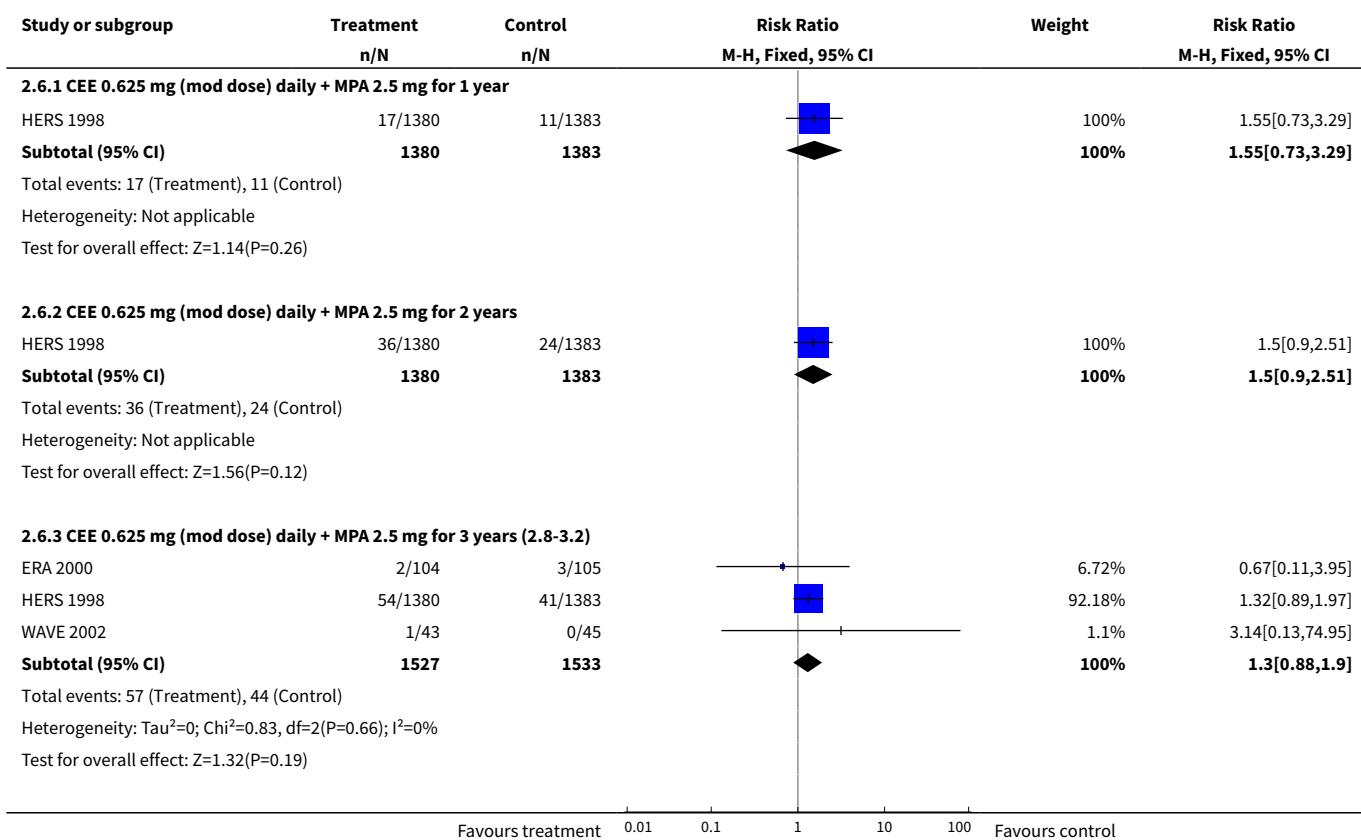


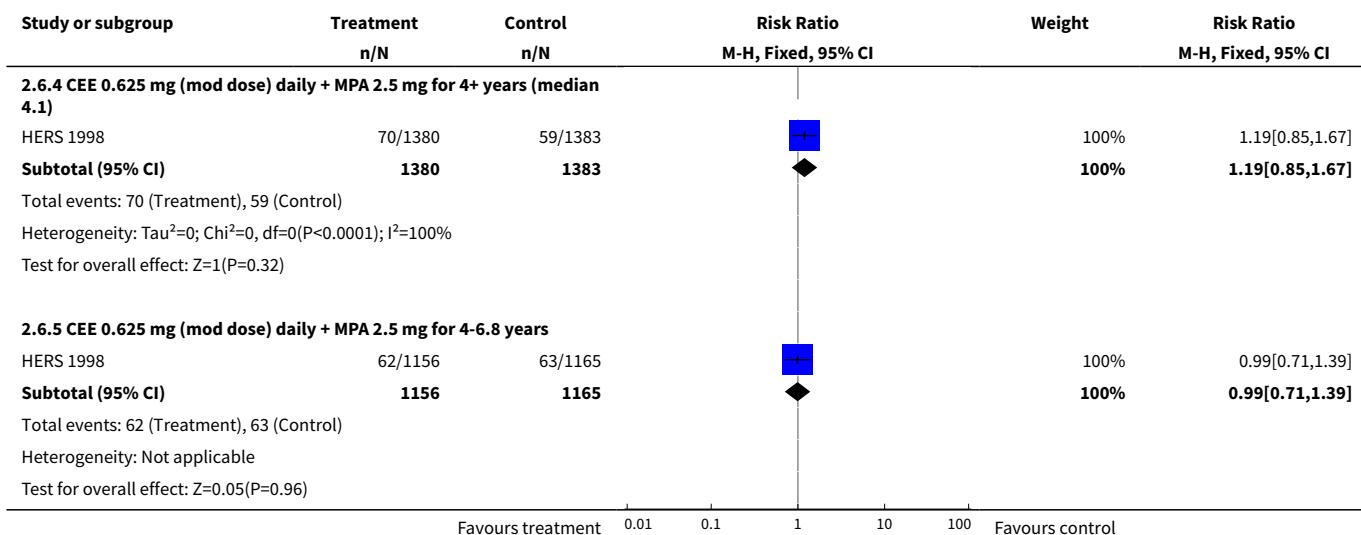


Analysis 2.5. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 5 Death from CHD: oestrogen-only or combined sequential HT.

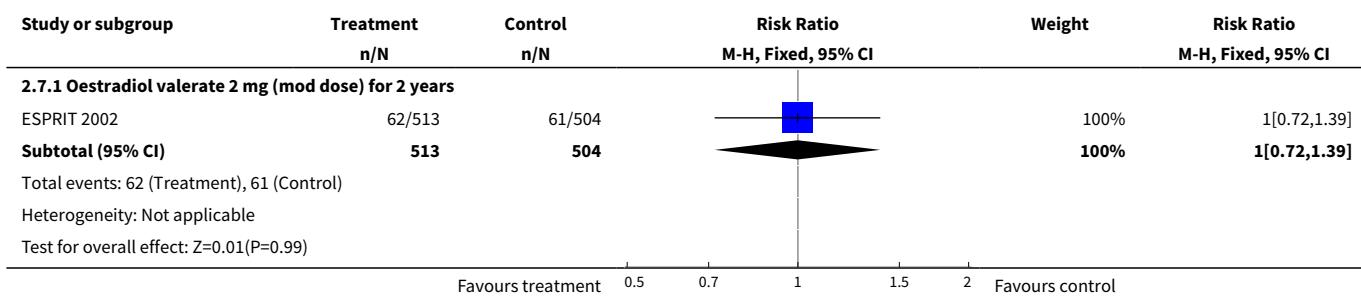


Analysis 2.6. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 6 Death from CHD: combined continuous HT.

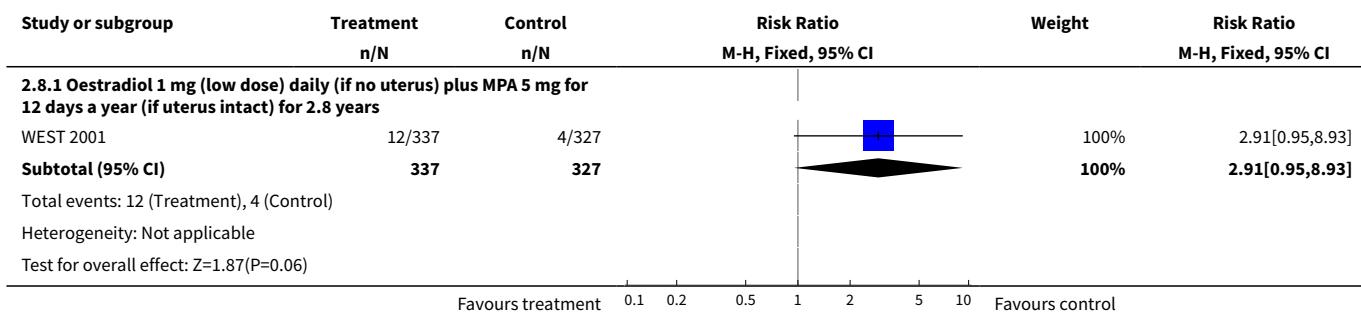


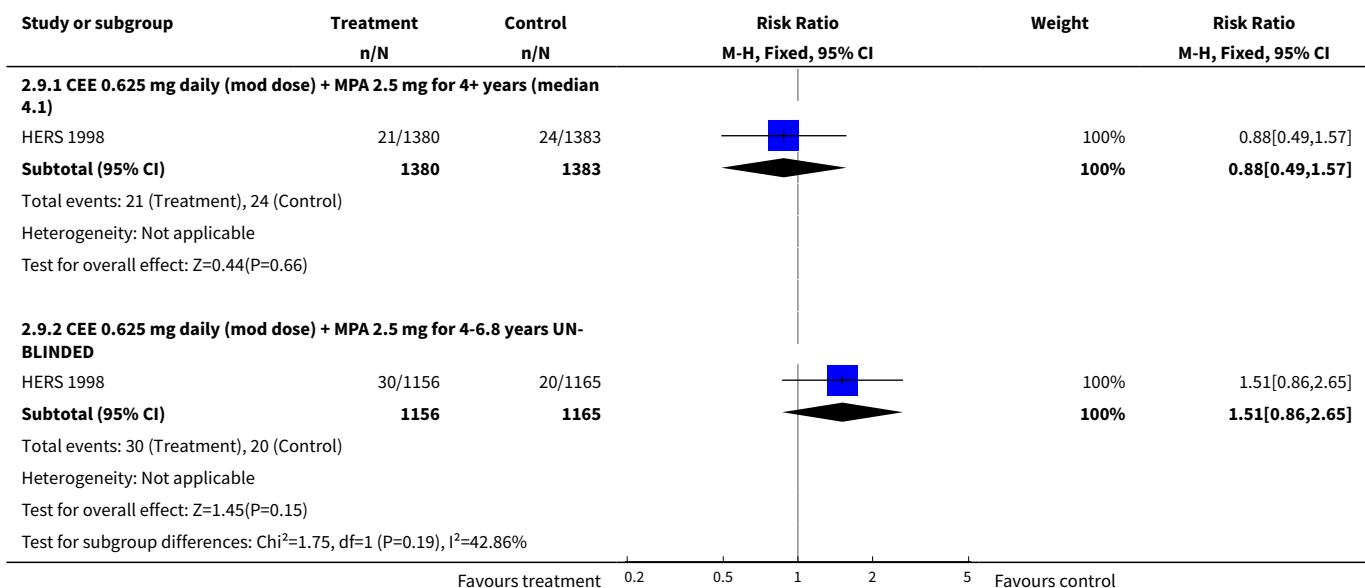
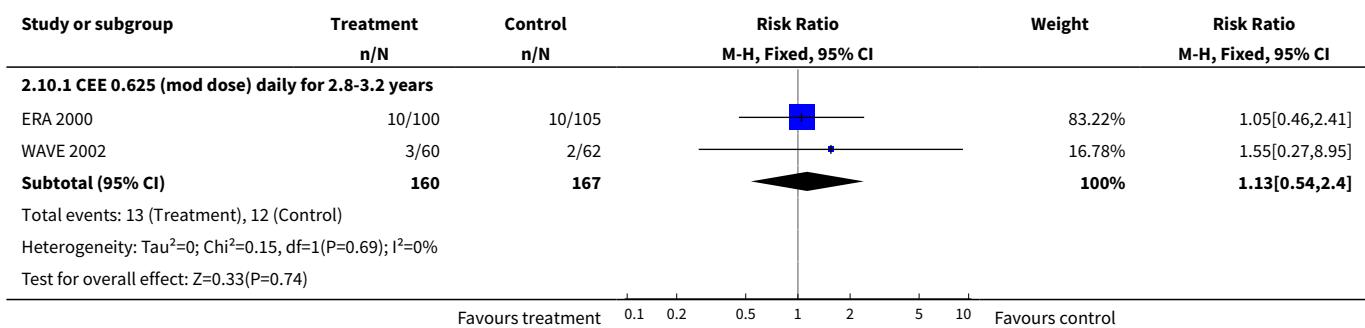
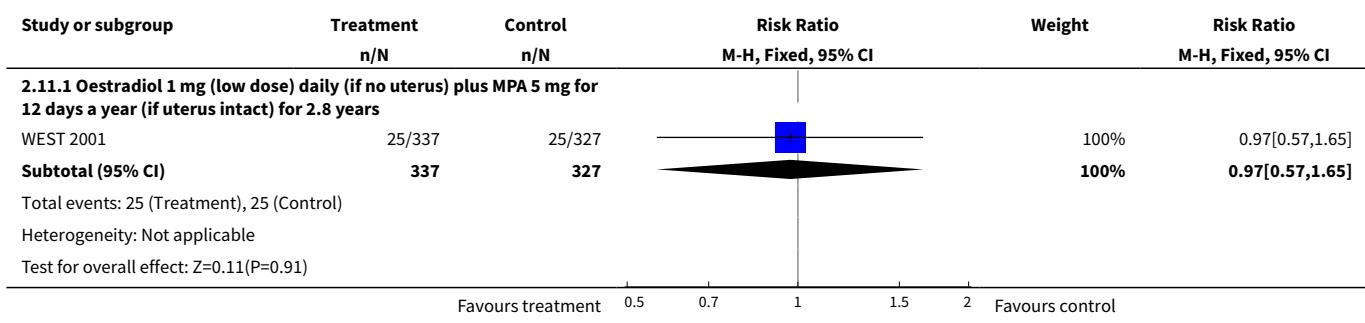


Analysis 2.7. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 7 Coronary event (MI or cardiac death): oestrogen-only HT.

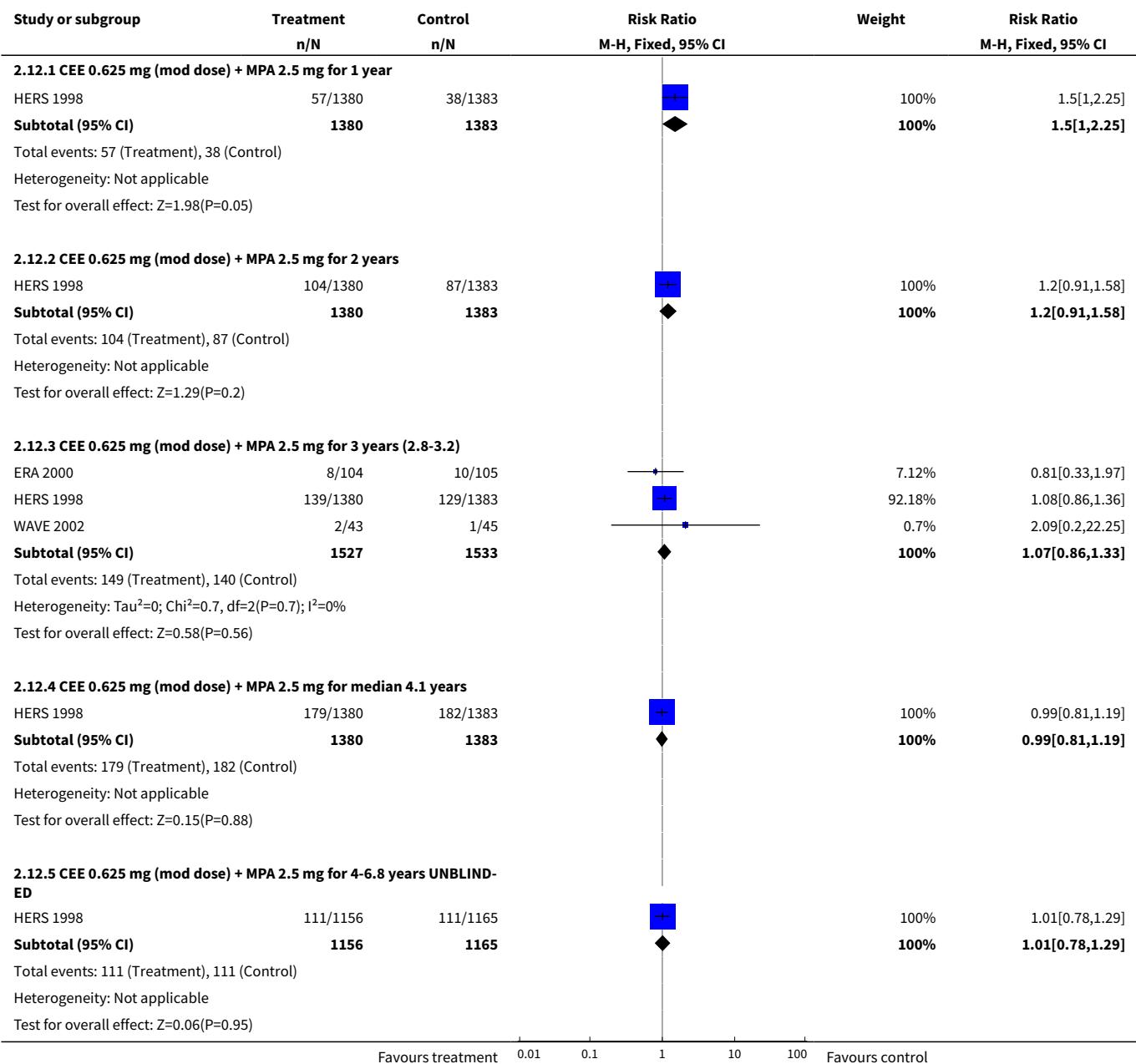


Analysis 2.8. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 8 Death from stroke: oestrogen-only or combined sequential HT.

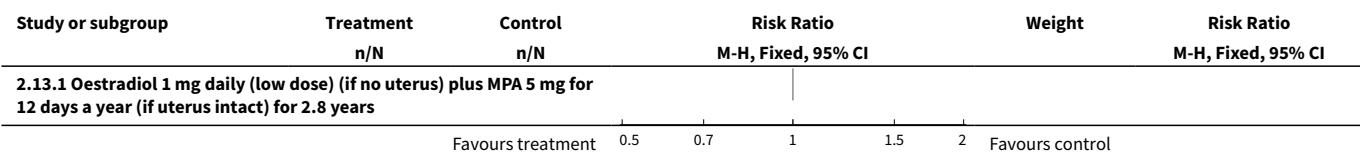


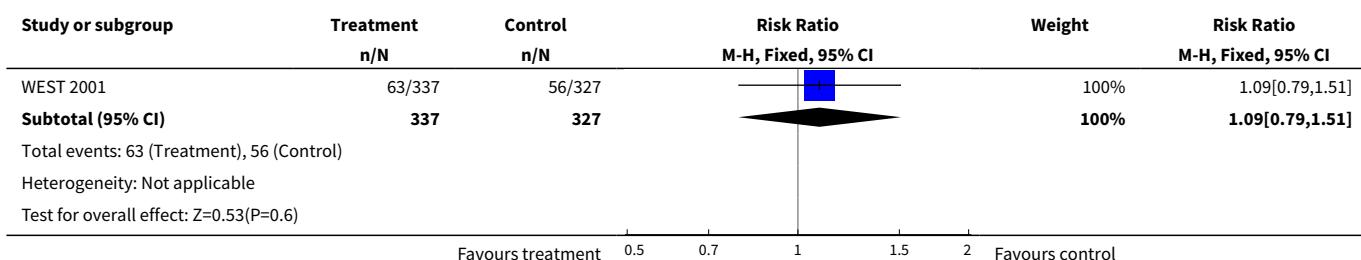
Analysis 2.9. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 9 Death from cancer: combined continuous HT.

Analysis 2.10. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 10 Coronary event (MI or cardiac death): oestrogen-only HT.

Analysis 2.11. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 11 Coronary event: oestrogen-only or combined sequential HT.


Analysis 2.12. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 12 Coronary event (MI or cardiac death): combined continuous HT.

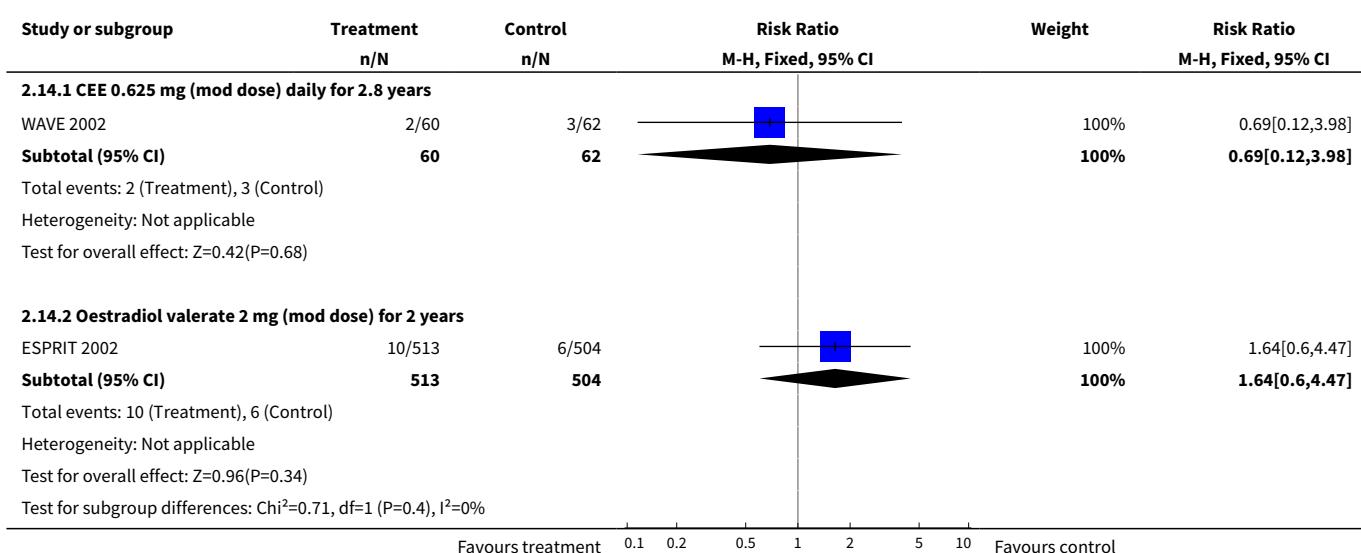


Analysis 2.13. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 13 Stroke (first or recurrent): oestrogen-only HT or combined sequential.

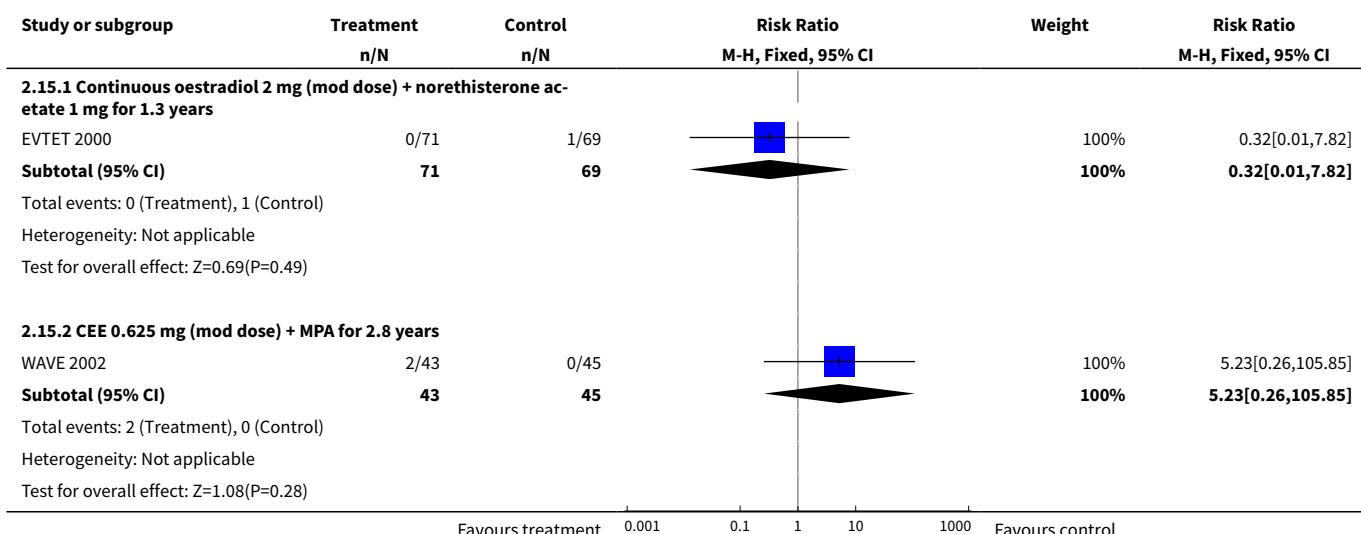


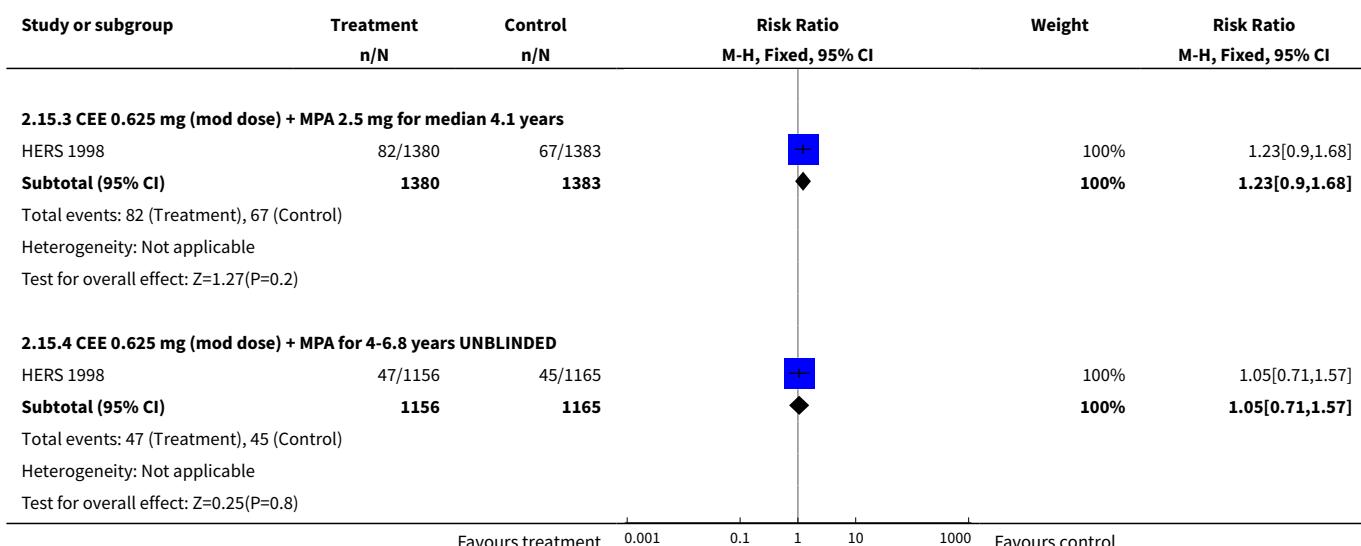


Analysis 2.14. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 14 Stroke (first or recurrent): oestrogen-only HT (mod dose).

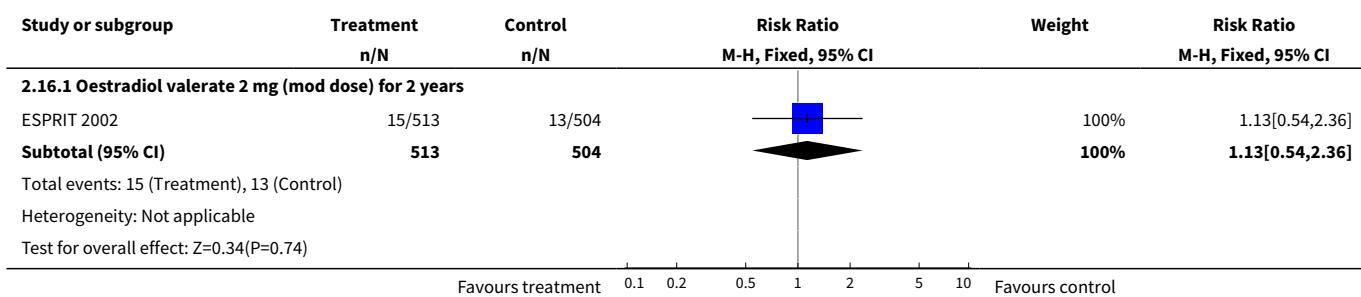


Analysis 2.15. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 15 Stroke (first or recurrent): combined continuous HT (mod dose oestrogen).

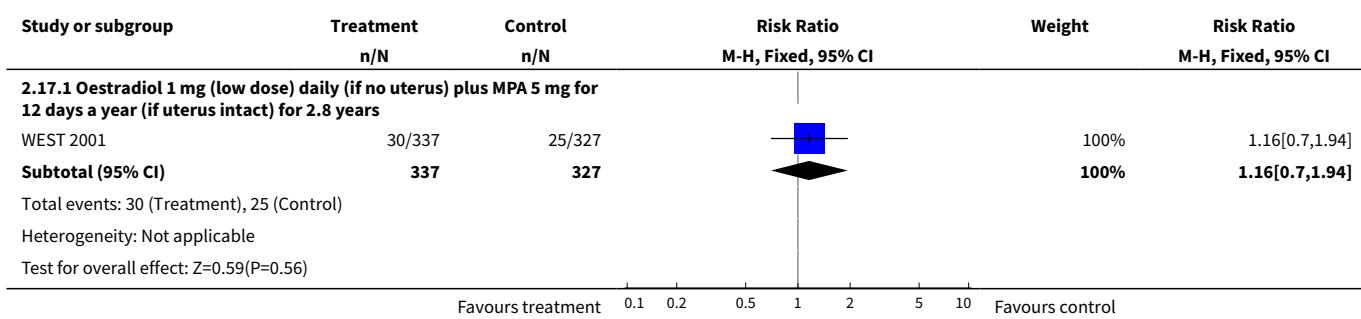




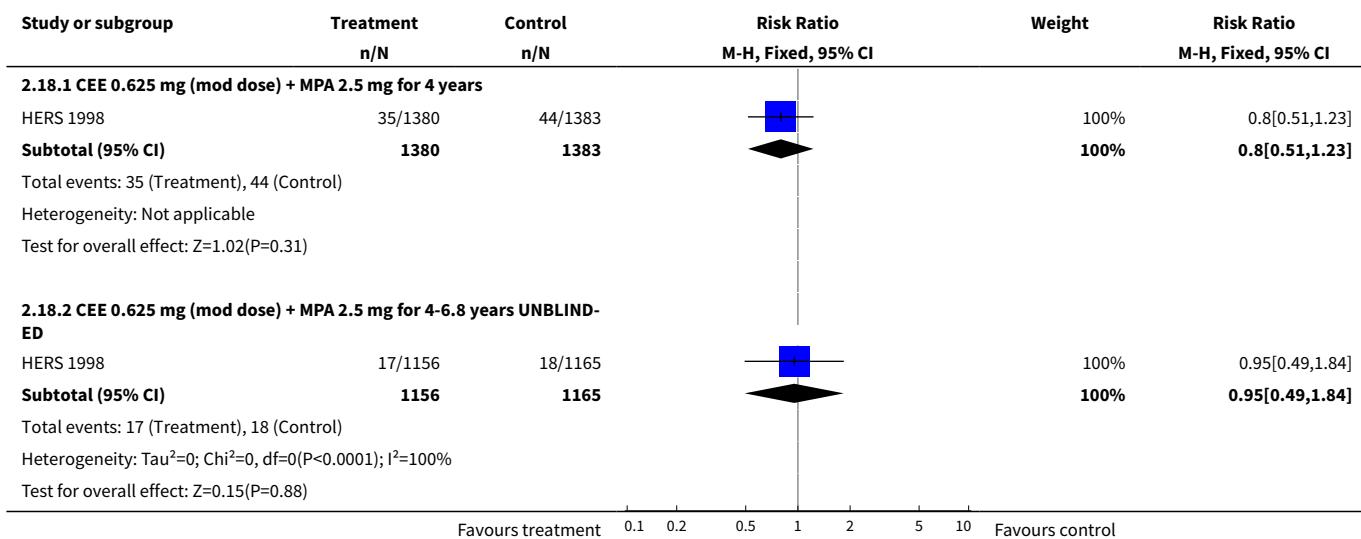
Analysis 2.16. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 16 Transient ischaemic attack: oestrogen-only HT (mod dose).



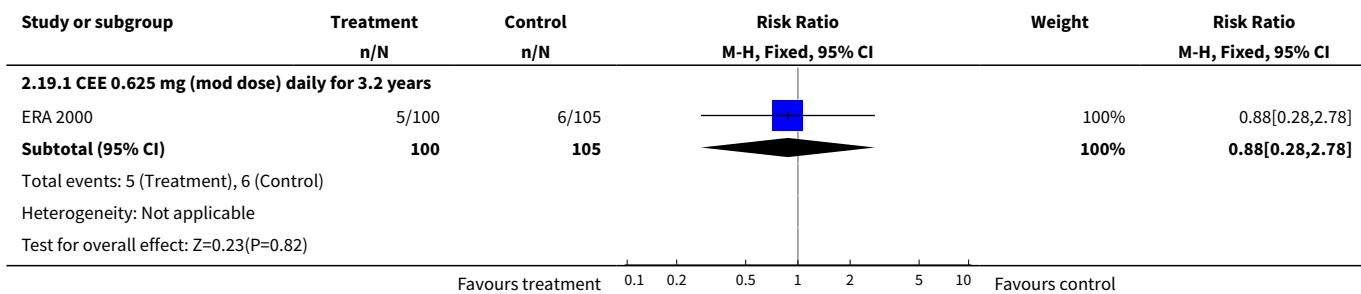
Analysis 2.17. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 17 Transient ischaemic attack: oestrogen-only or combined sequential HT.



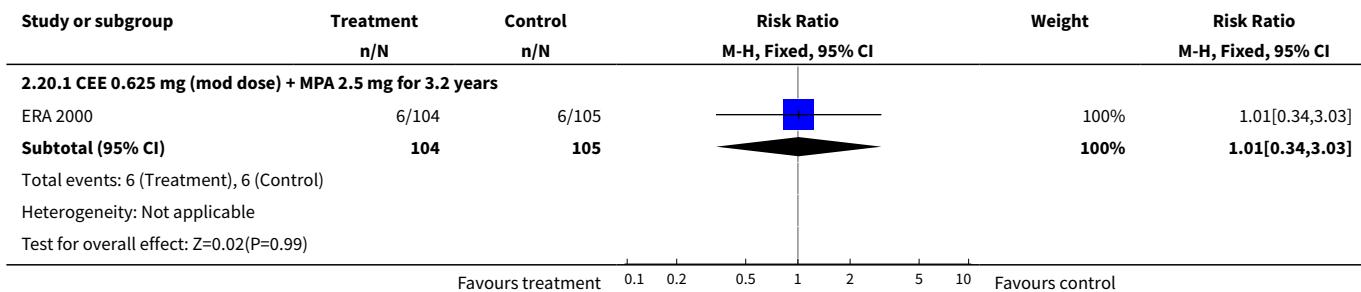
Analysis 2.18. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 18 Transient ischaemic attack: combined continuous HT.



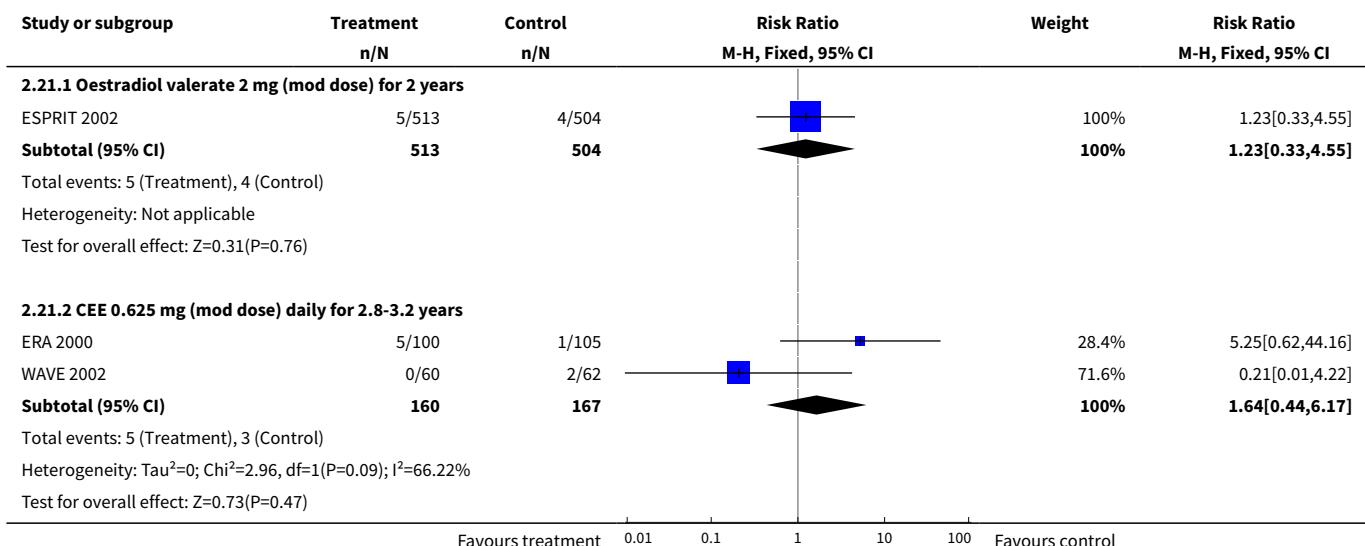
Analysis 2.19. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 19 Stroke or transient ischaemic attack: oestrogen-only HT.



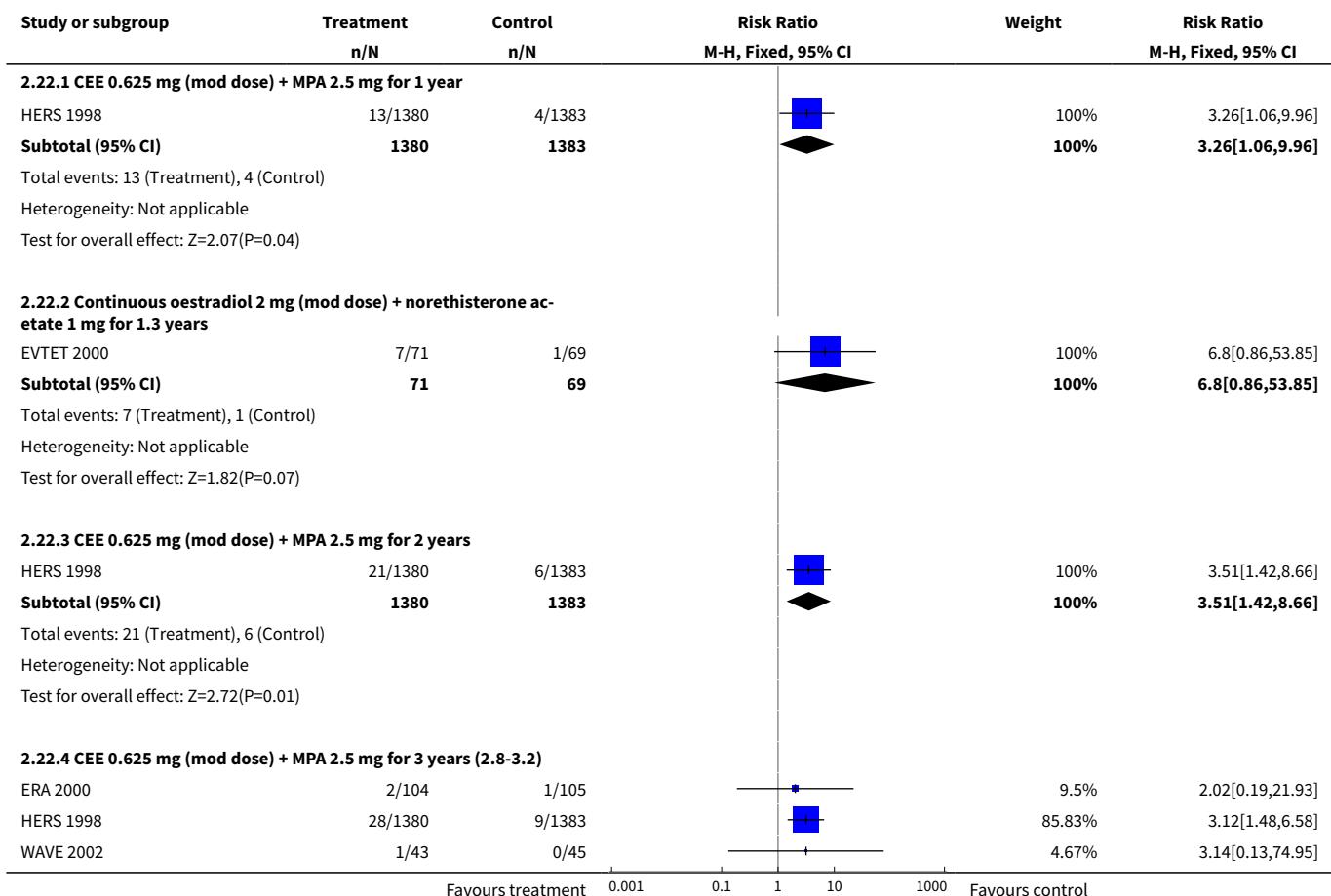
Analysis 2.20. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 20 Stroke or transient ischaemic attack: combined continuous HT.

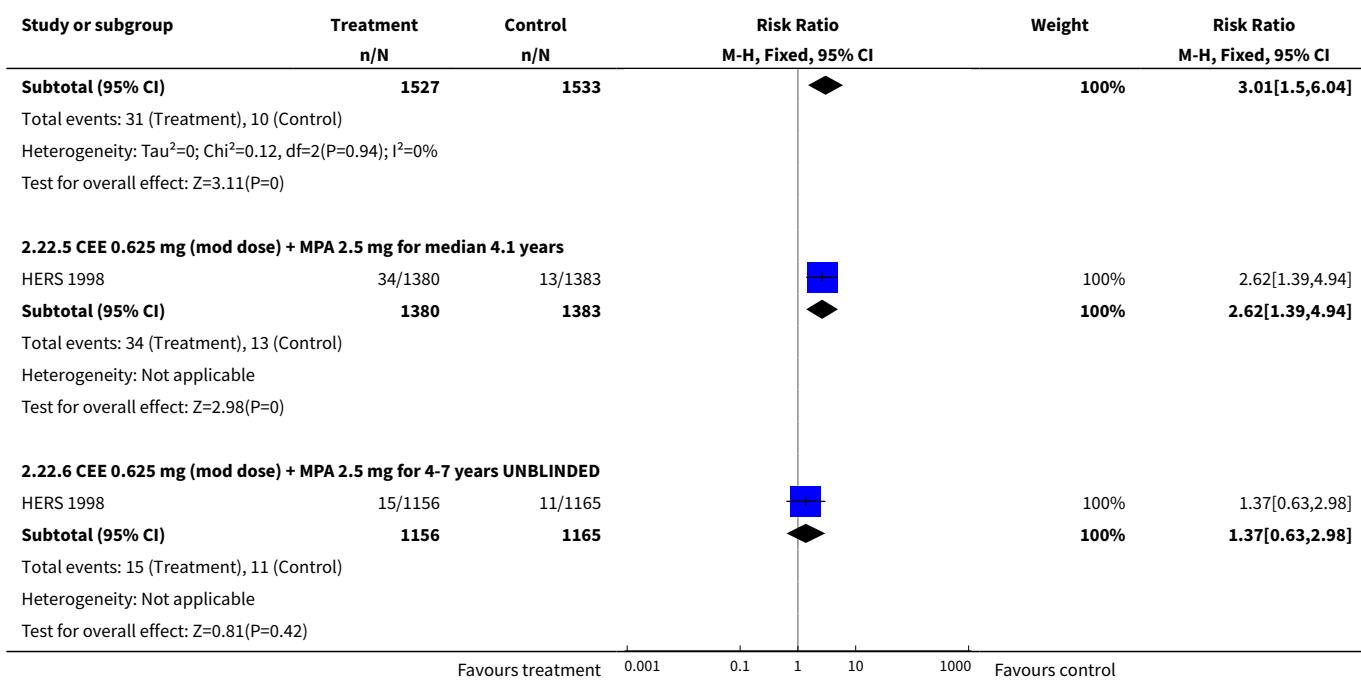


Analysis 2.21. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 21 VTE (first or recurrent PE or DVT): oestrogen-only HT.



Analysis 2.22. Comparison 2 Women with cardiovascular disease (selected outcomes: death, CVD, cognition, QOL), Outcome 22 VTE (first or recurrent PE or DVT): combined continuous HT.

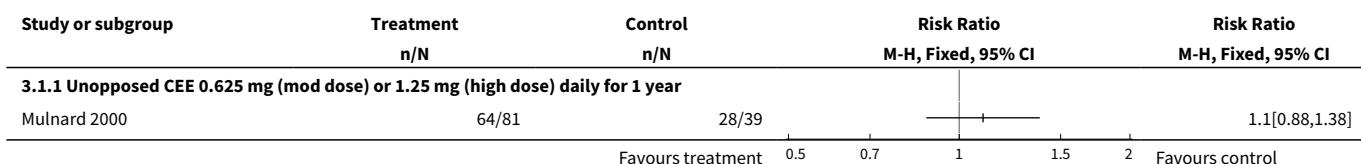




Comparison 3. Women with dementia

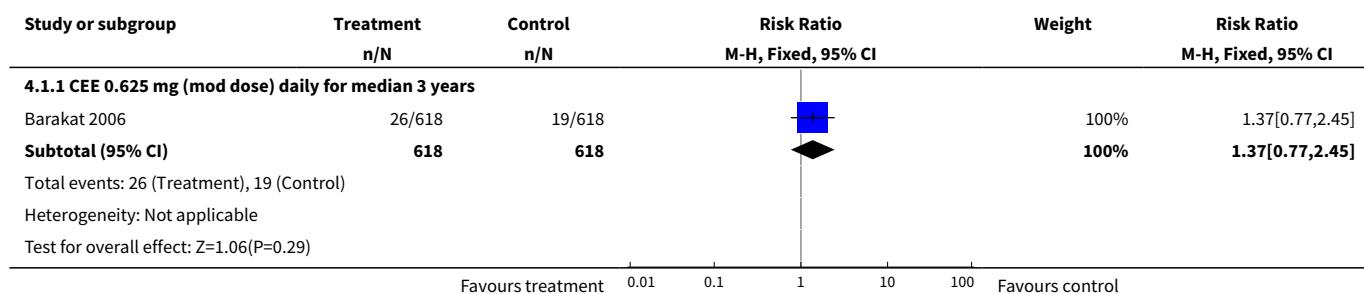
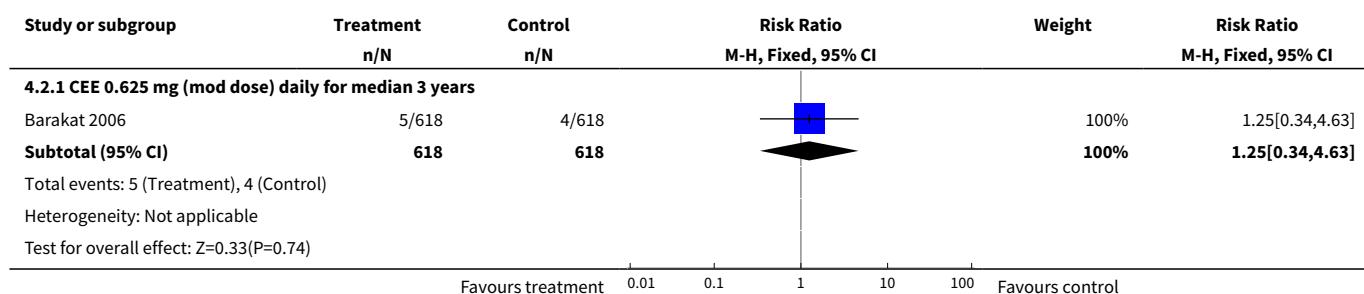
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worsening of dementia on treatment (by ADCS-CGIC score): oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Unopposed CEE 0.625 mg (mod dose) or 1.25 mg (high dose) daily for 1 year	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Women with dementia, Outcome 1 Worsening of dementia on treatment (by ADCS-CGIC score): oestrogen-only HT.

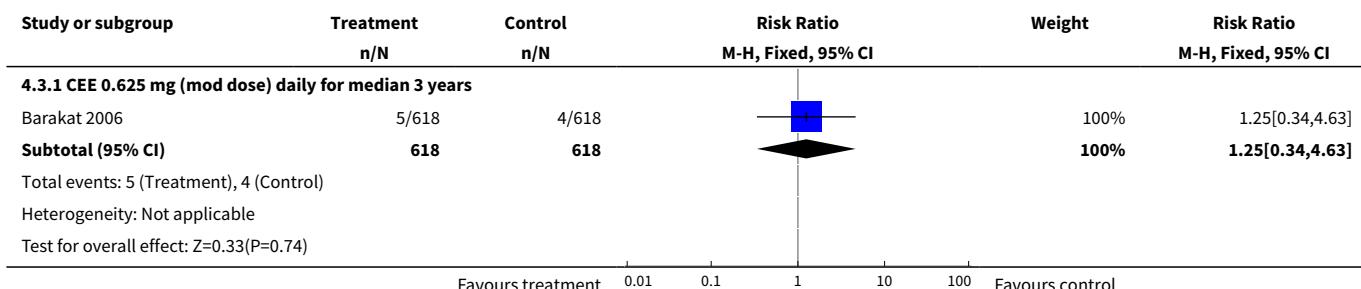


Comparison 4. Women post surgery for early-stage endometrial cancer (selected outcomes: death, recurrence)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from any cause: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CEE 0.625 mg (mod dose) daily for median 3 years	1	1236	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.77, 2.45]
2 Death from endometrial cancer: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CEE 0.625 mg (mod dose) daily for median 3 years	1	1236	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.34, 4.63]
3 Death from CHD: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 CEE 0.625 mg (mod dose) daily for median 3 years	1	1236	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.34, 4.63]

Analysis 4.1. Comparison 4 Women post surgery for early-stage endometrial cancer (selected outcomes: death, recurrence), Outcome 1 Death from any cause: oestrogen-only HT.

Analysis 4.2. Comparison 4 Women post surgery for early-stage endometrial cancer (selected outcomes: death, recurrence), Outcome 2 Death from endometrial cancer: oestrogen-only HT.


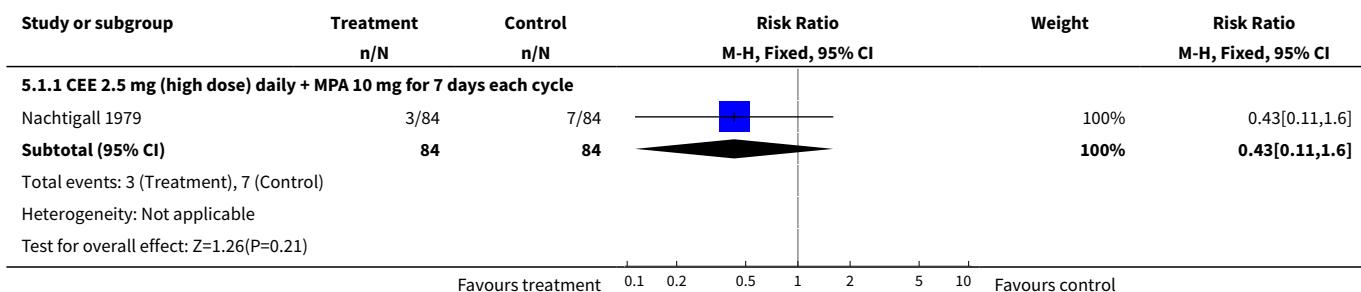
**Analysis 4.3. Comparison 4 Women post surgery for early-stage endometrial cancer
(selected outcomes: death, recurrence), Outcome 3 Death from CHD: oestrogen-only HT.**



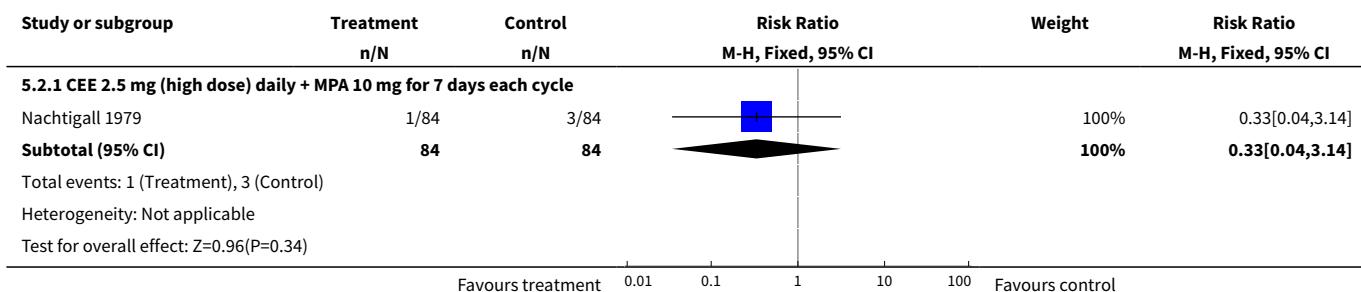
Comparison 5. Women hospitalised with chronic illness (selected outcomes: death, CVD, VTE)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause death: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CEE 2.5 mg (high dose) daily + MPA 10 mg for 7 days each cycle	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.11, 1.60]
2 Myocardial infarction: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CEE 2.5 mg (high dose) daily + MPA 10 mg for 7 days each cycle	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.14]
3 Venous thromboembolism (DVT or PE): combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 CEE 2.5 mg (high dose) daily + MPA 10 mg for 7 days each cycle	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.07]

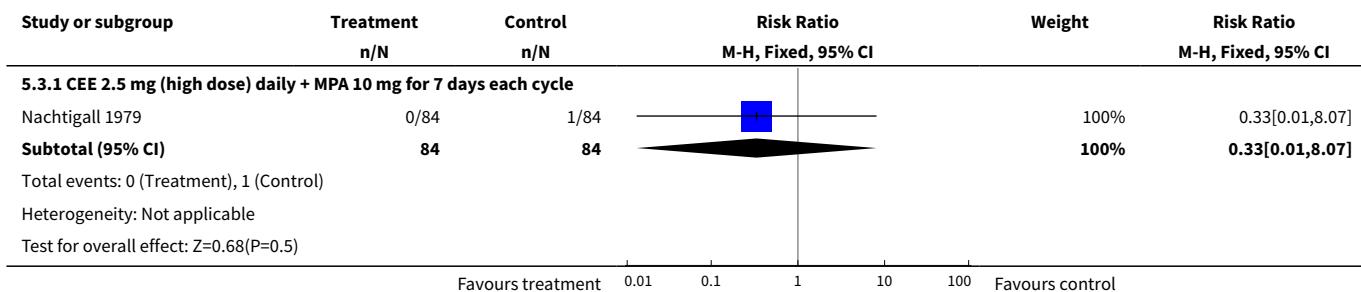
Analysis 5.1. Comparison 5 Women hospitalised with chronic illness (selected outcomes: death, CVD, VTE), Outcome 1 All-cause death: combined sequential HT.



Analysis 5.2. Comparison 5 Women hospitalised with chronic illness (selected outcomes: death, CVD, VTE), Outcome 2 Myocardial infarction: combined sequential HT.



Analysis 5.3. Comparison 5 Women hospitalised with chronic illness (selected outcomes: death, CVD, VTE), Outcome 3 Venous thromboembolism (DVT or PE): combined sequential HT.



Comparison 6. All women (selected outcomes: cancer, cholecytic disease, fractures)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breast cancer: oestrogen-only HT	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oestrogen only HRT patch 0.025 (low dose) mg daily for 2 years	1	176	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.04]
1.2 Oestradiol 1 mg (low dose) for 2 years	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
1.3 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.25, 3.91]
1.4 Oestradiol patch 0.075 mg (high dose) for 2 years	1	176	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.04]
1.5 CEE 0.625 mg (mod dose) for 2.8-3.2 years	3	676	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.38, 11.04]
1.6 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 CEE 0.625 mg (mod dose) after 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.63, 0.96]
1.8 CEE 0.625 mg (mod dose) after 13 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.97]
2 Breast cancer: oestrogen-only or combined HT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 CEE 0.625 mg (mod dose) with or without 2.5 mg MPA for 3 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Breast cancer: combined continuous HT	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	23182	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.96]
3.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.47, 1.08]
3.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2.8-3.4 years	3	17733	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.18]
3.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.27]
3.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.03, 1.56]
3.6 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-7 years unblinded	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.52, 2.23]
3.7 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 7.9 years	1	16607	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.07, 1.52]
3.8 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 11 years (includes extra follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.08, 1.45]
3.9 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended follow up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.11, 1.47]
4 Breast cancer: combined sequential HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 21.85]
4.2 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	352	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [0.44, 34.64]
4.3 CEE 0.045 mg (lowish dose) + 200 mg sequential progesterone for 4 years	1	505	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.30, 10.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Oestradiol patch 0.05 mg (mod dose) + 200 mg sequential progesterone for 4 years	1	497	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.31, 11.02]
4.5 CEE 2.5 mg daily (high dose) + MPA 10 mg for 7 days each cycle for 10 years	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.03]
5 Breast cancer: oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.10]
6 Colorectal cancer: oestrogen-only HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 CEE 0.625 mg (mod dose) for 3 years	1	349	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.08]
6.2 CEE 0.625 (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.81, 1.63]
6.3 CEE 0.625 mg (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.49]
7 Colorectal cancer: oestrogen-only or combined HT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 CEE 0.625 mg (mod dose) with or without 2.5 mg MPA for 3 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Colorectal cancer: combined continuous HT	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.32, 1.42]
8.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.50]
8.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years	2	16956	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.49, 1.34]
8.4 CEE 0.625 mg (mod dose) + 2.5 mg MPA for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.32, 1.48]
8.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.91]
8.6 CEE 0.625 mg (mod dose) + 2.5 mg MPA for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.44]
8.7 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 7.9 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.57, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.8 CEE 0.0625 mg (mod dose) + MPA 2.5 mg after 11.6 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 0.99]
8.9 CEE 0.0625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.01]
9 Colorectal cancer: combined sequential HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
9.2 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	352	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]
9.3 CEE 2.5 mg (high dose) daily + MPA 10 mg for 7 days each cycle for 10 years	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.73]
10 Colorectal cancer: oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.25, 8.83]
11 Lung cancer: oestrogen-only HT (moderate dose)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Any lung cancer (non-small cell or small cell) at 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.48]
12 Lung cancer: combined continuous HT (mod dose oestrogen)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Any lung cancer at 5.6 years (non-small cell or small cell)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.46]
12.2 Any lung cancer at 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.92, 1.62]
12.3 Any lung cancer after median 14 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.38]
13 Lung cancer: combined sequential HT	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 17-B-oestradiol 1 mg (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [0.13, 78.13]
14 Endometrial cancer: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 CEE 0.625 mg (mod dose) for 3-3.2 years	1	238	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
15 Endometrial cancer: combined continuous HT (moderate dose oestrogen)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 CEE 0.625 mg + MPA 2.5 mg for 1 year	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.13, 6.76]
15.2 CEE 0.625 mg + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.31, 2.95]
15.3 CEE 0.625 mg + MPA 2.5 mg for 3-3.2 years	2	16847	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.35, 1.82]
15.4 CEE 0.625 mg + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.06]
15.5 CEE 0.625 mg + MPA 2.5 mg for 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.51, 1.44]
15.6 CEE 0.625 mg + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.78]
15.7 CEE 0.625 + MPS 2.5 mg for 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.20]
15.8 CEE 0.625 mg + MPA 2.5 mg after median 13 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.48, 0.90]
16 Endometrial cancer: combined sequential HT	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 17-B-oestradiol 1 mg (low dose) + dydrogesterone 5 mg days 14-28 for 2 years	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.08, 45.95]
16.2 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	239	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.03]
16.3 Oestradiol 2 mg (mod dose) + dihydrogesterone 20 mg for 2 years	1	159	Risk Ratio (M-H, Fixed, 95% CI)	3.30 [0.16, 67.59]
16.4 CEE 0.045 mg (lowish dose) + 200 mg sequential progesterone for 4 years	1	505	Risk Ratio (M-H, Fixed, 95% CI)	5.97 [0.29, 123.81]
16.5 Oestradiol patch 0.05 mg (mod dose) + 200 mg sequential progesterone for 4 years	1	497	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.15, 90.70]
16.6 CEE 2.5 mg (high dose) daily + MPA 10 mg for 7 days each cycle for 10 years	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.07]
17 Recurrent endometrial cancer: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

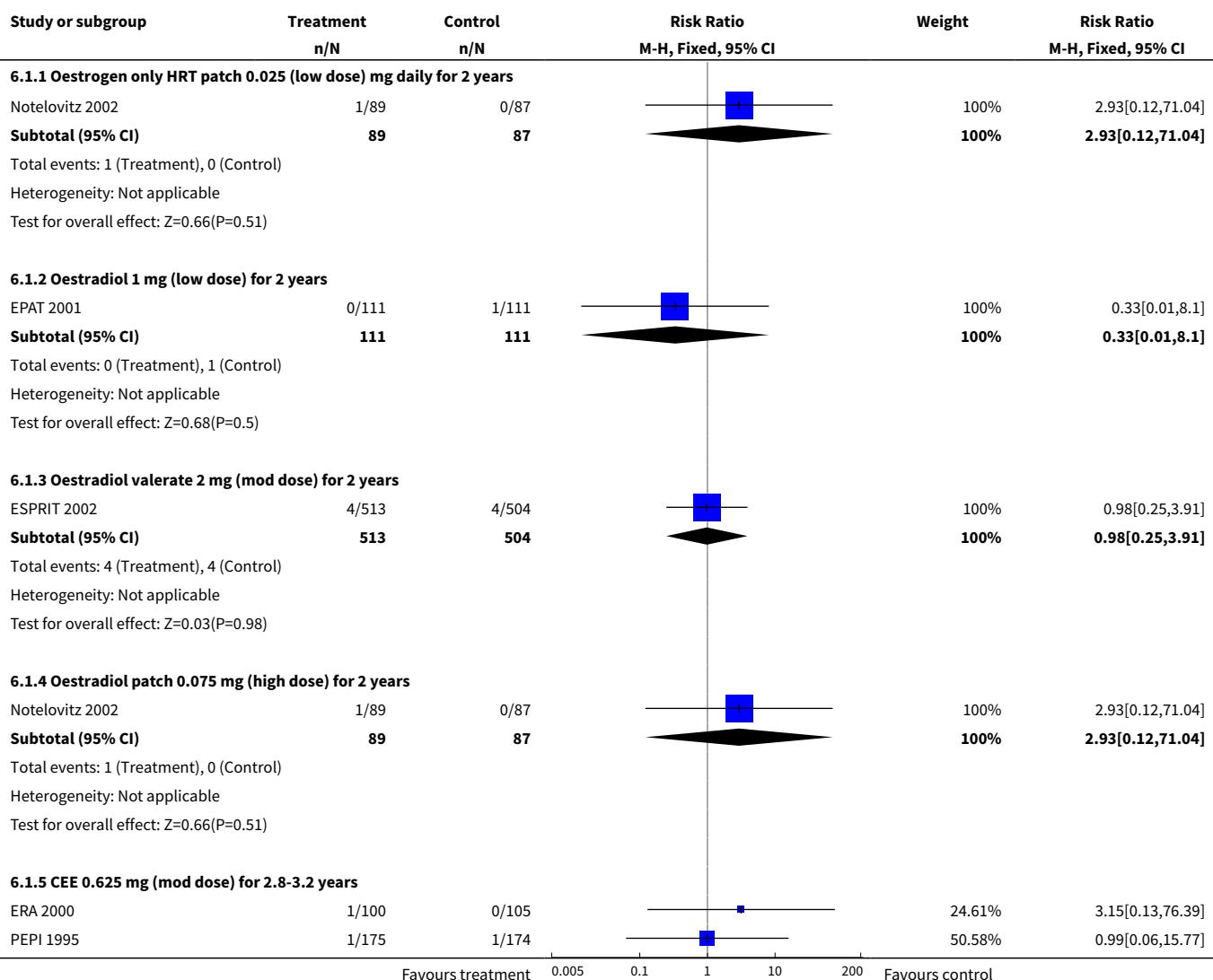
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Oestrogen (type and dose not stated) for median 3 years	1	1236	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.54, 2.50]
18 Ovarian cancer: combined continuous HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.76, 2.69]
18.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg after 13.2 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.82, 1.85]
19 Ovarian cancer: oestrogen with or without sequential progesterone vaginal gel	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Oestradiol 1 mg daily, with or without cyclic 4% vaginal progesterone gel	1	643	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.08]
20 Gallbladder disease requiring surgery: oestrogen-only HT	3	8930	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.40, 2.19]
20.1 CEE 0.625 mg (mod dose) for 3-3.2 years	2	554	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.17, 3.39]
20.2 CEE 0.625 mg (mod dose) for 7.1 years	1	8376	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.42, 2.24]
21 Gallbladder disease requiring surgery: combined continuous HT	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 CEE 0.625 mg (mod dose) + 2.5 mg MPA for 3 years	2	557	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.61, 6.59]
21.2 CEE 0.625 mg (mod dose) + 2.5 mg MPA for 4 years	1	2253	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.85]
21.3 CEE 0.625 mg (mod dose) + 2.5 mg MPA for mean 5.6 years	1	14203	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.30, 2.06]
22 Gallbladder disease requiring surgery: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 CEE 0.625 mg (mod dose) daily + MPA 10 mg days 1-12 for 3 years	1	348	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.37, 10.78]
22.2 CEE 0.625 mg (mod dose) daily + micronised progesterone 200 mg days 1-12 for 3 years	1	352	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.25, 8.67]
23 Hip fractures: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.46, 0.95]

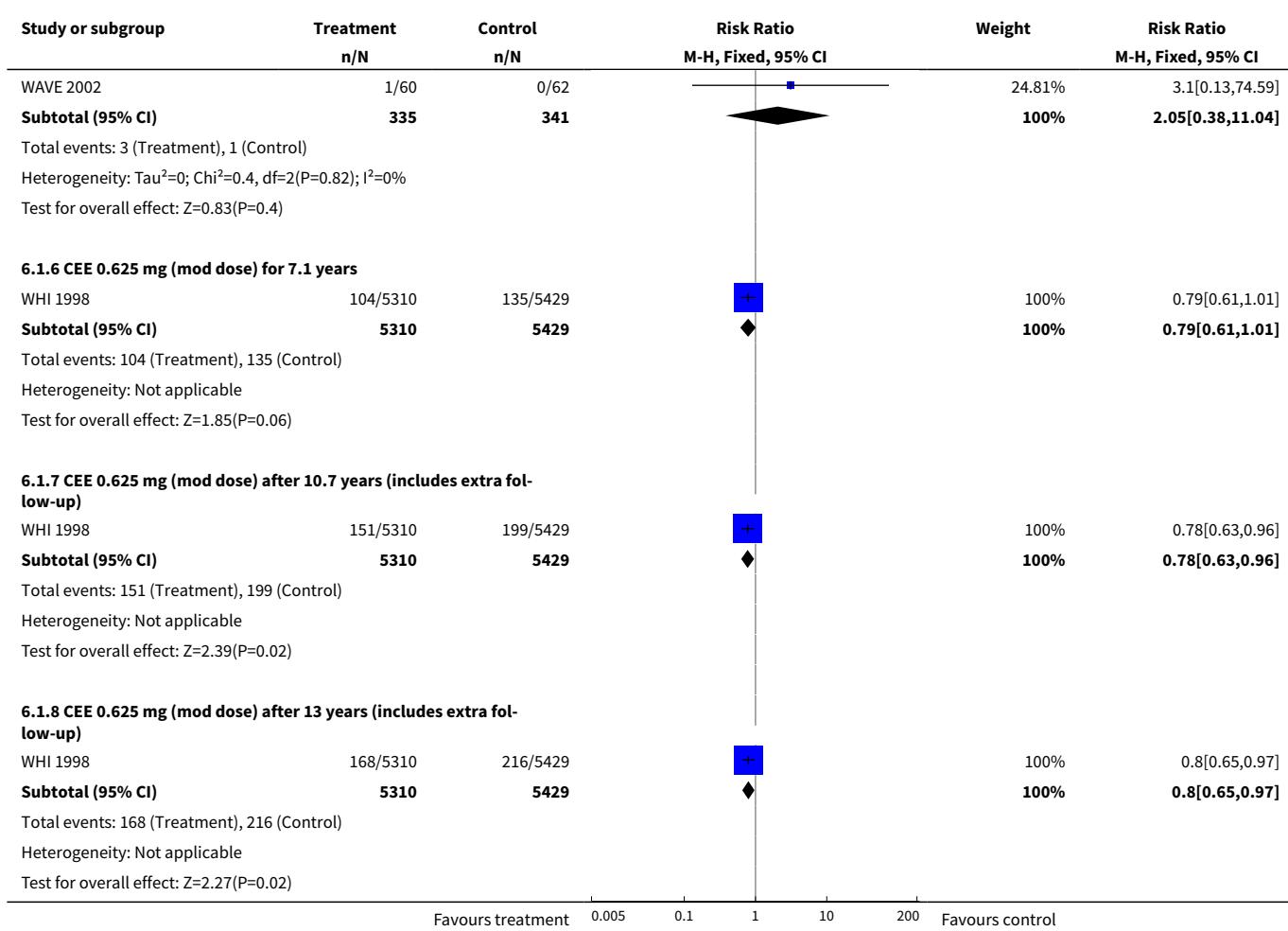
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.2 CEE 0.625 mg (mod dose) for 10.7 years (includes extra follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.18]
23.3 CEE 0.625 mg (mod dose) after 13.2 years (includes extended follow-up)	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.74, 1.17]
24 Hip fractures: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.27, 1.42]
25 Hip fractures: combined continuous HT	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean/median 1 year	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.26, 1.57]
25.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 2 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.31, 1.18]
25.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.42, 1.17]
25.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.55, 2.42]
25.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.96]
25.6 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.06, 4.16]
25.7 CEE 0.625 mg (mod dose) + 2.5 mg MPA for 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.99]
25.8 CEE 0.625 mg (mod dose) + 2.5 mg MPA after 13.2 years (includes extended follow-up)	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.97]
26 Hip fractures: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 17-B-oestradiol 1 mg (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.27]
27 Vertebral fractures: oestrogen-only HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28 Vertebral fractures: combined continuous HT	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.37, 1.47]
28.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.49, 0.96]
28.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.49, 2.48]
28.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.01]
29 All clinical fractures: oestrogen-only or combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Oestradiol 1 mg (low dose) daily (if no uterus) plus MPA 5 mg for 12 days a year (if uterus intact) for 2.8 years	1	664	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.68, 2.19]
30 All clinical fractures: oestrogen-only HT (moderate dose)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Oestradiol valerate 2 mg (mod dose) for 2 years	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.26]
30.2 CEE 0.625 mg (mod dose) daily for 3.2 years	1	205	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.04]
30.3 CEE 0.625 mg (mod dose) for 7.1 years	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.65, 0.80]
31 All clinical fractures: oestrogen-only or combined HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
31.1 CEE 0.625 mg (mod dose) with or without 2.5 mg MPA for 3 years	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 All clinical fractures: combined continuous HT	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 CEE 0.625 mg (mod dose) + MPA 2.5 mg for median 1 year	1	4385	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.46, 1.02]
32.2 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 3.2-3.4 years	2	986	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.32, 0.87]
32.3 CEE 0.625 mg (mod dose) + MPA 2.5 mg for mean 5.6 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.71, 0.86]
32.4 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4 years	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.18]

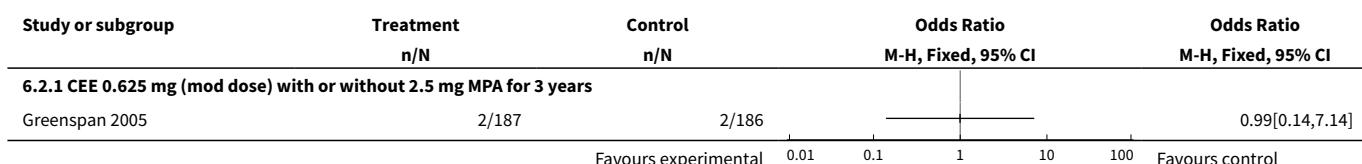
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.5 CEE 0.625 mg (mod dose) + MPA 2.5 mg for 4-6.8 years UNBLINDED	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.91, 1.65]
32.6 CEE 0.0625 mg (mod dose) + MPA 2.5 mg for mean 7.9 years	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.76, 0.89]
33 All clinical fractures: combined sequential HT	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 17-B-oestradiol 1 mg (low dose) daily plus (3 days weekly) 0.35 mg norethindrone for 2 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.12, 1.64]

Analysis 6.1. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 1 Breast cancer: oestrogen-only HT.

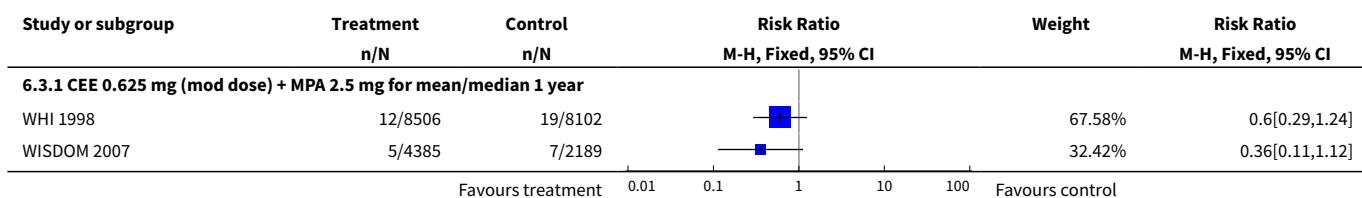


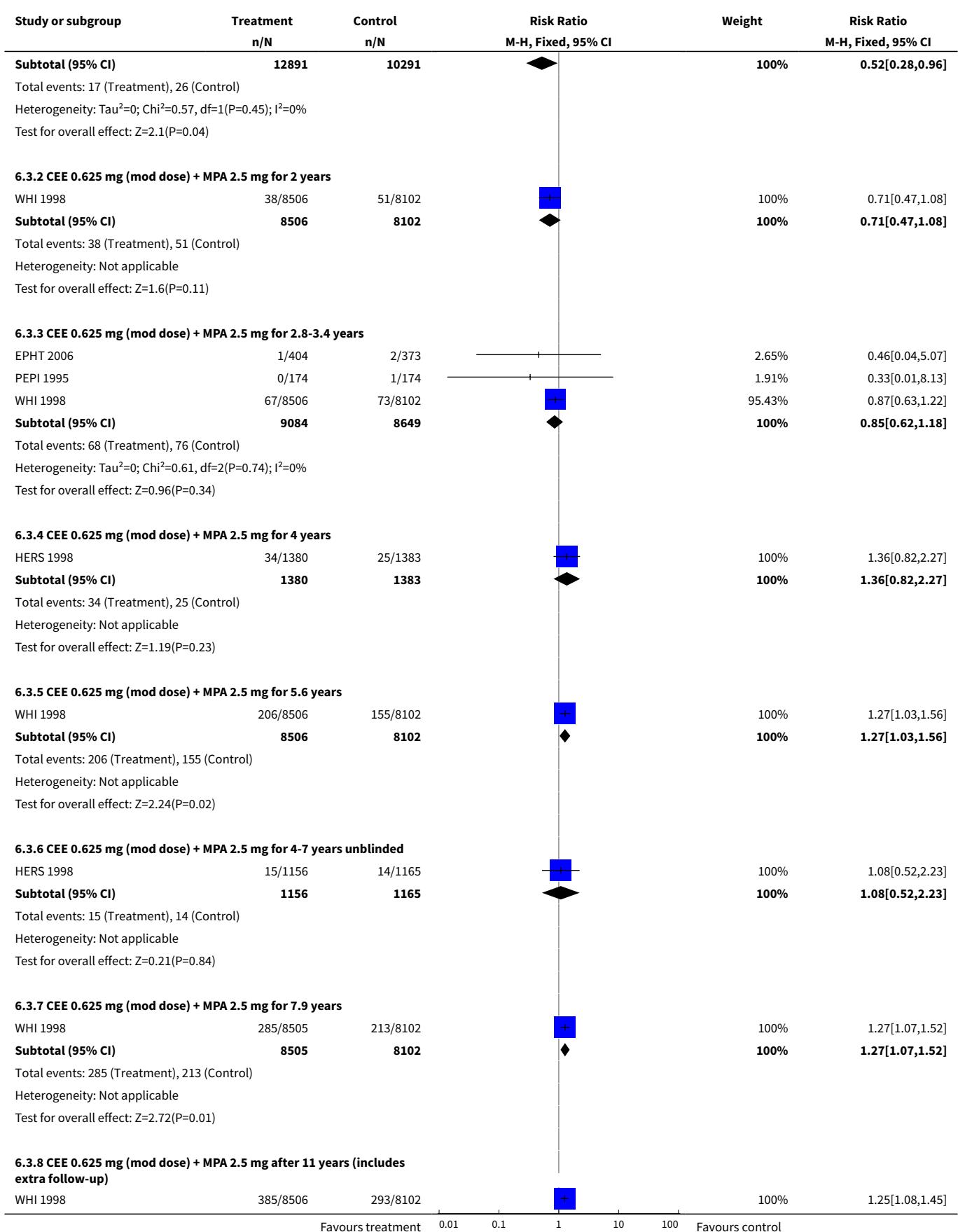


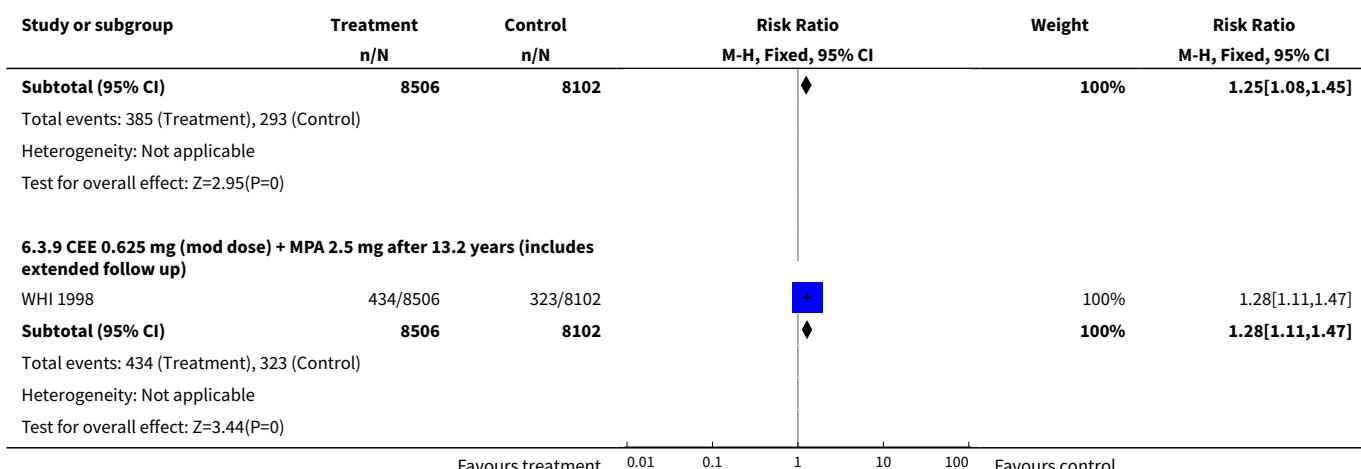
Analysis 6.2. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 2 Breast cancer: oestrogen-only or combined HT.



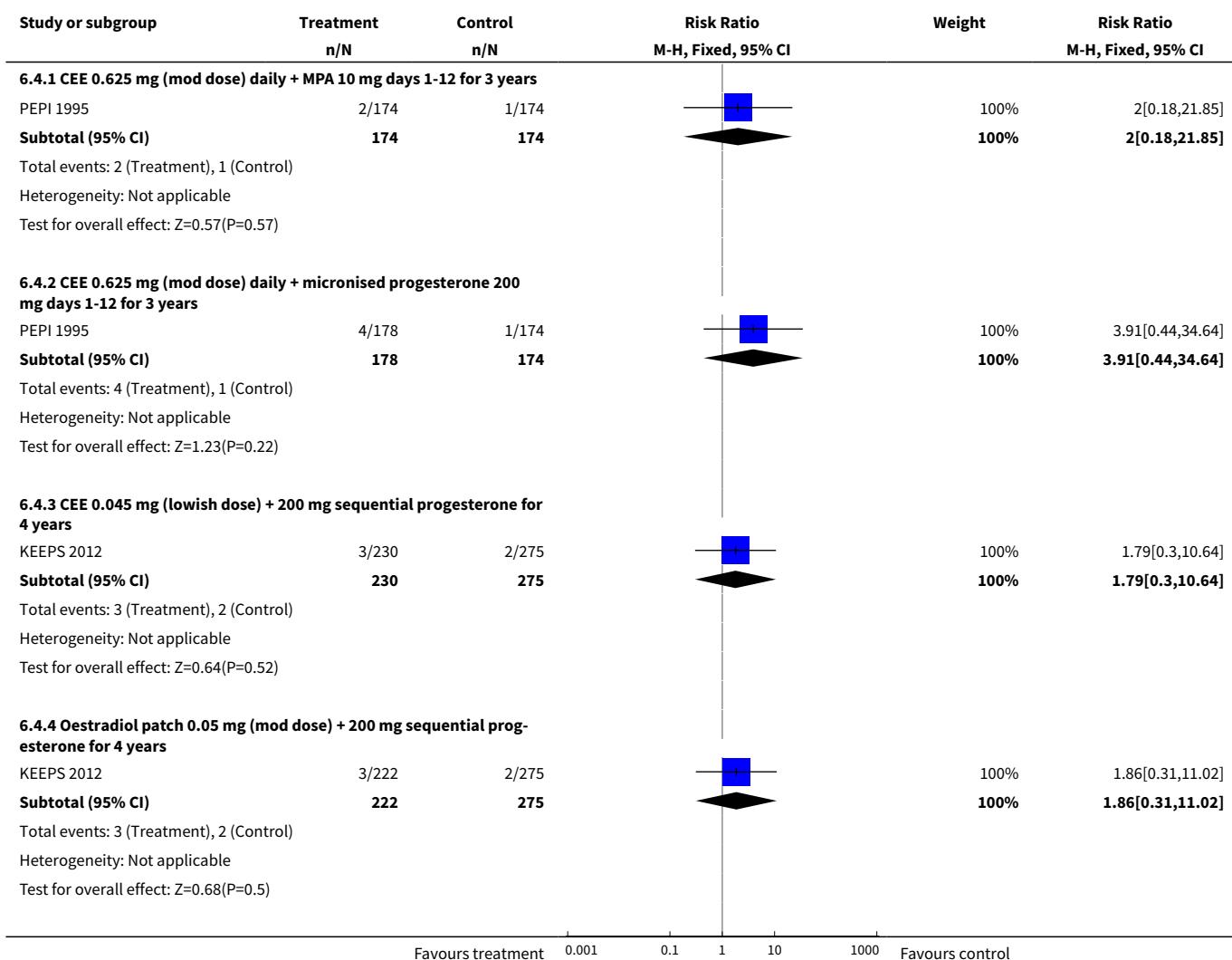
Analysis 6.3. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 3 Breast cancer: combined continuous HT.

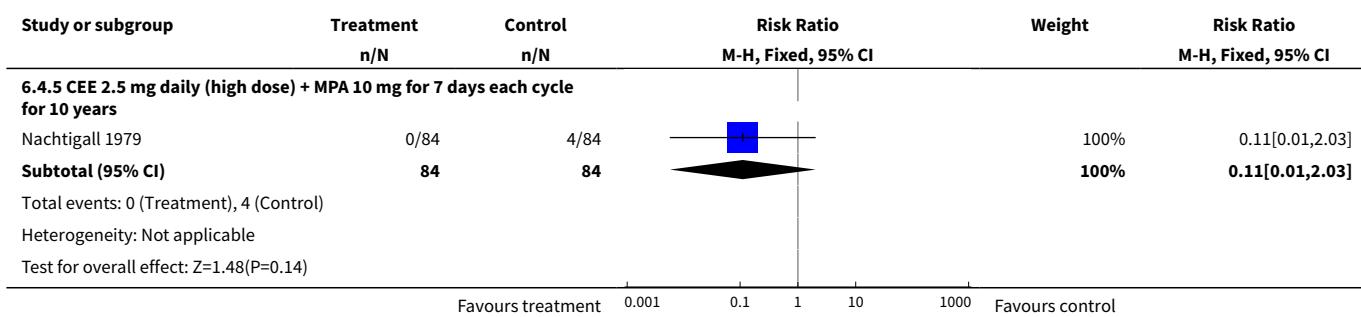




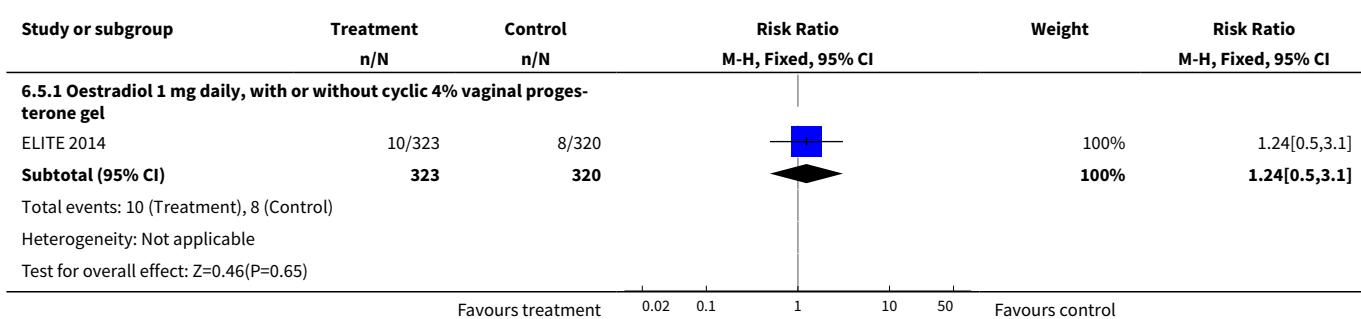


Analysis 6.4. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 4 Breast cancer: combined sequential HT.

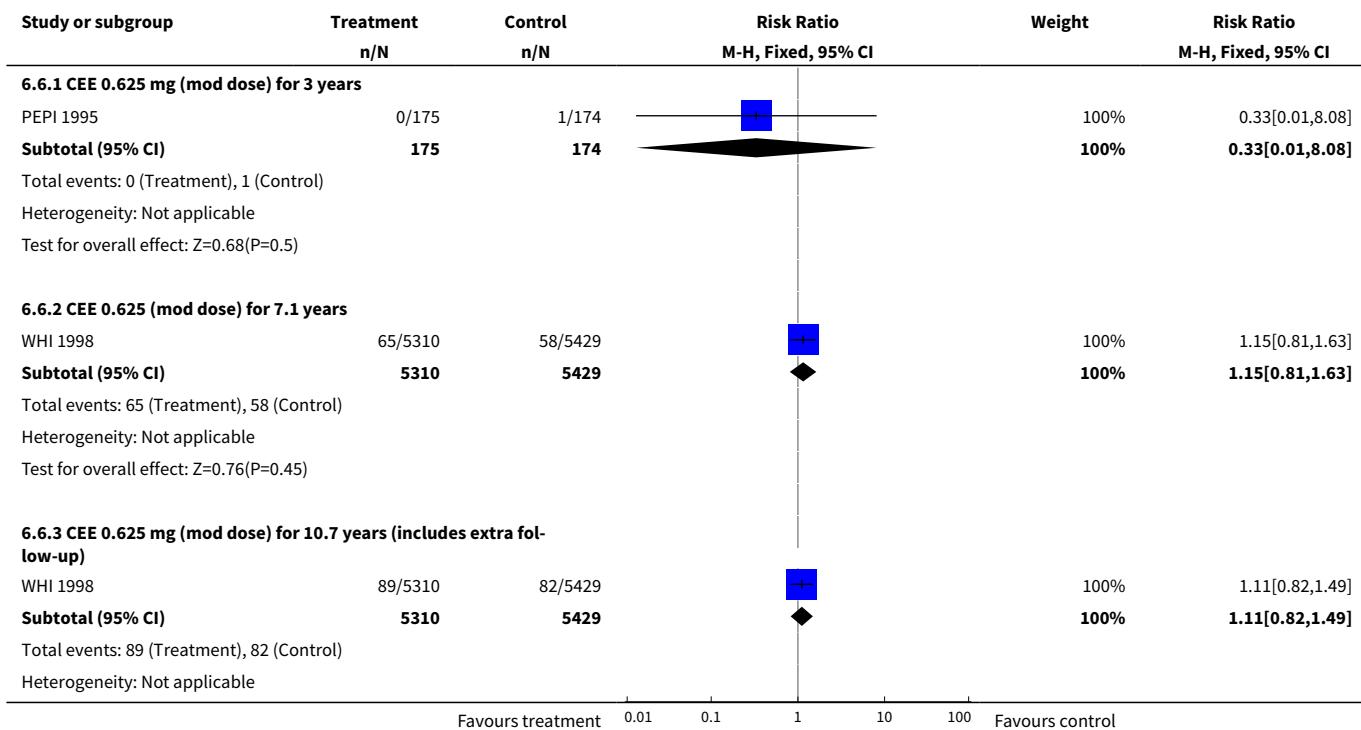


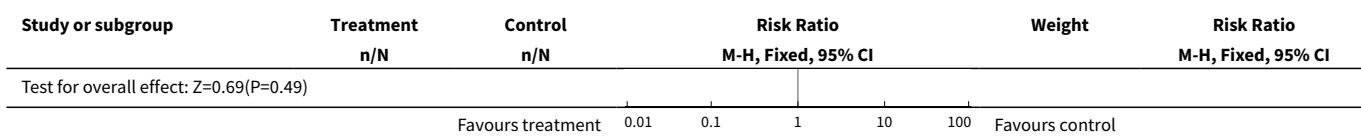


Analysis 6.5. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 5 Breast cancer: oestrogen with or without sequential progesterone vaginal gel.

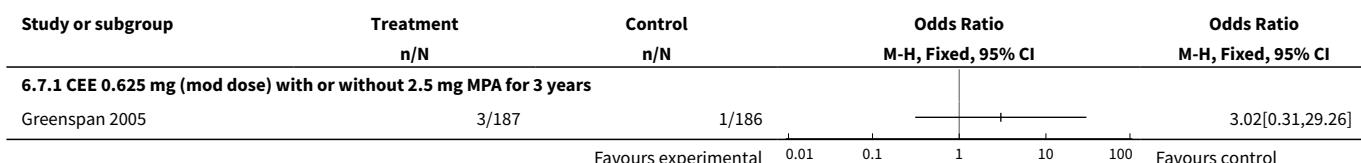


Analysis 6.6. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 6 Colorectal cancer: oestrogen-only HT.

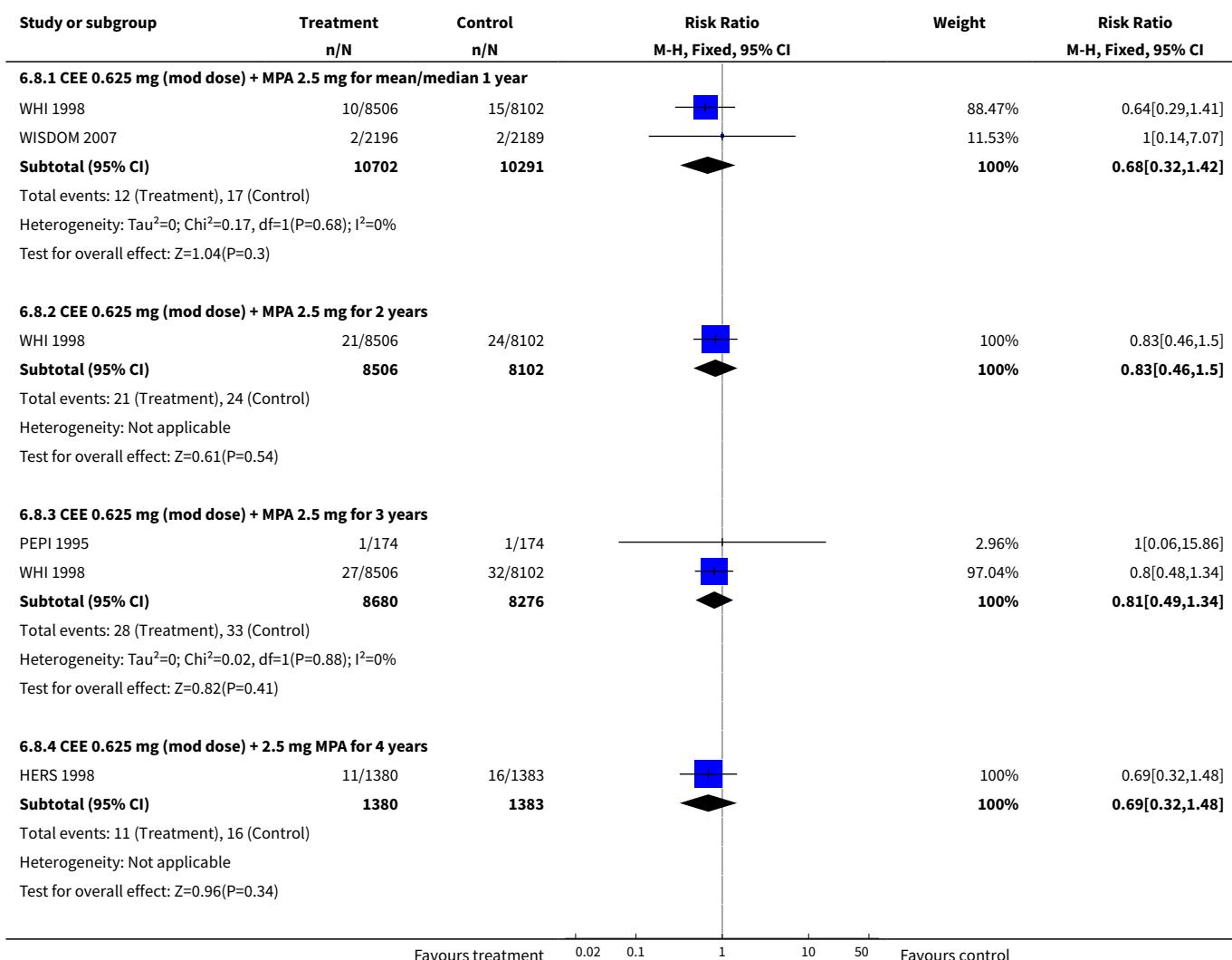


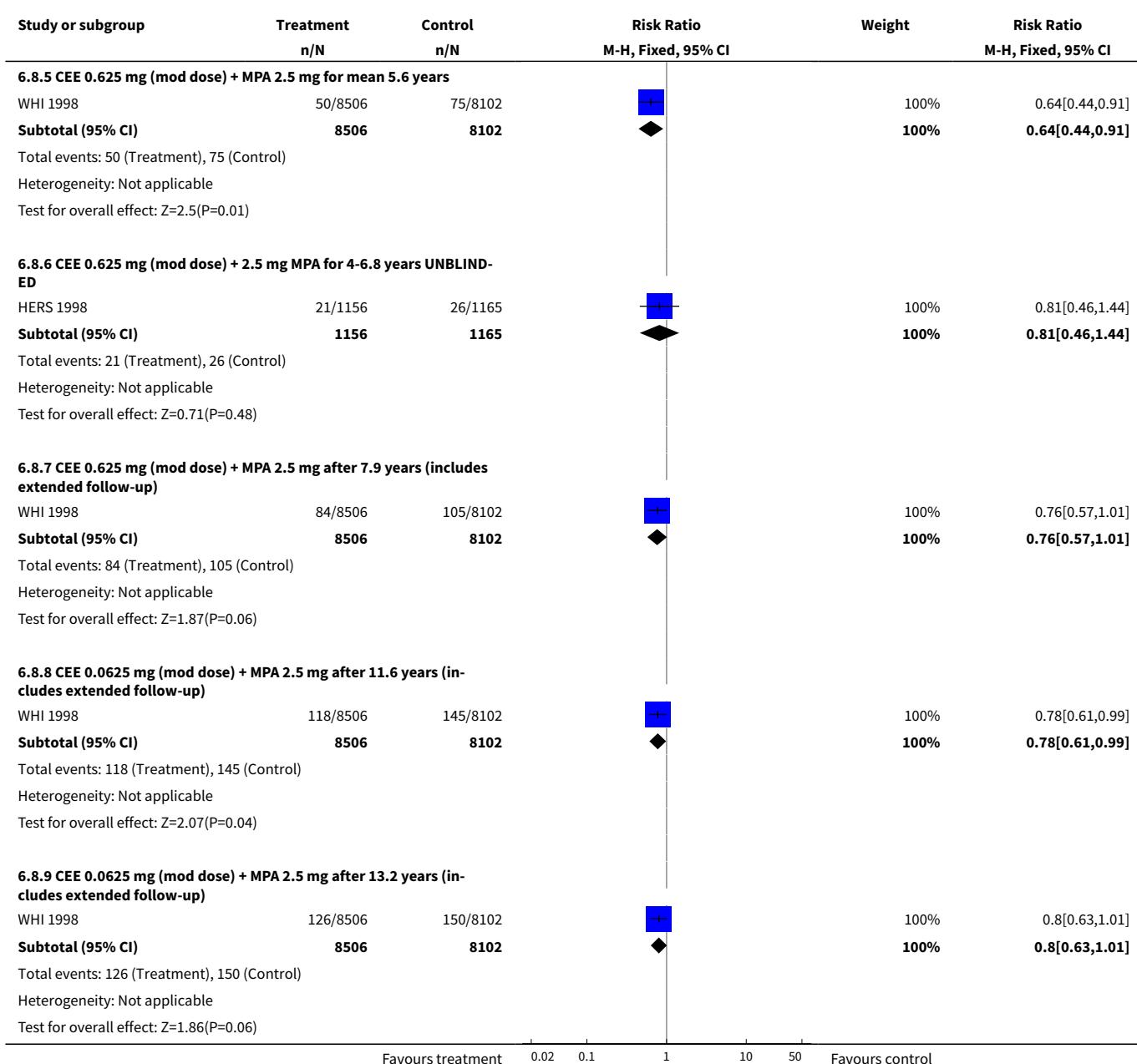


Analysis 6.7. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 7 Colorectal cancer: oestrogen-only or combined HT.

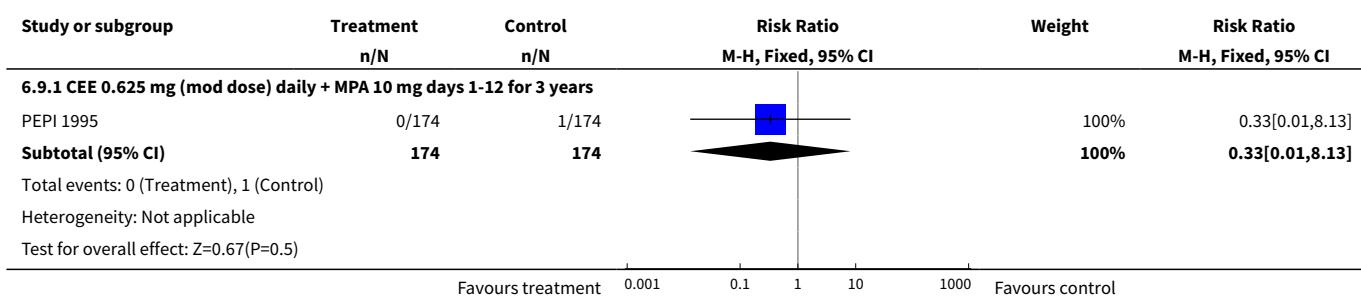


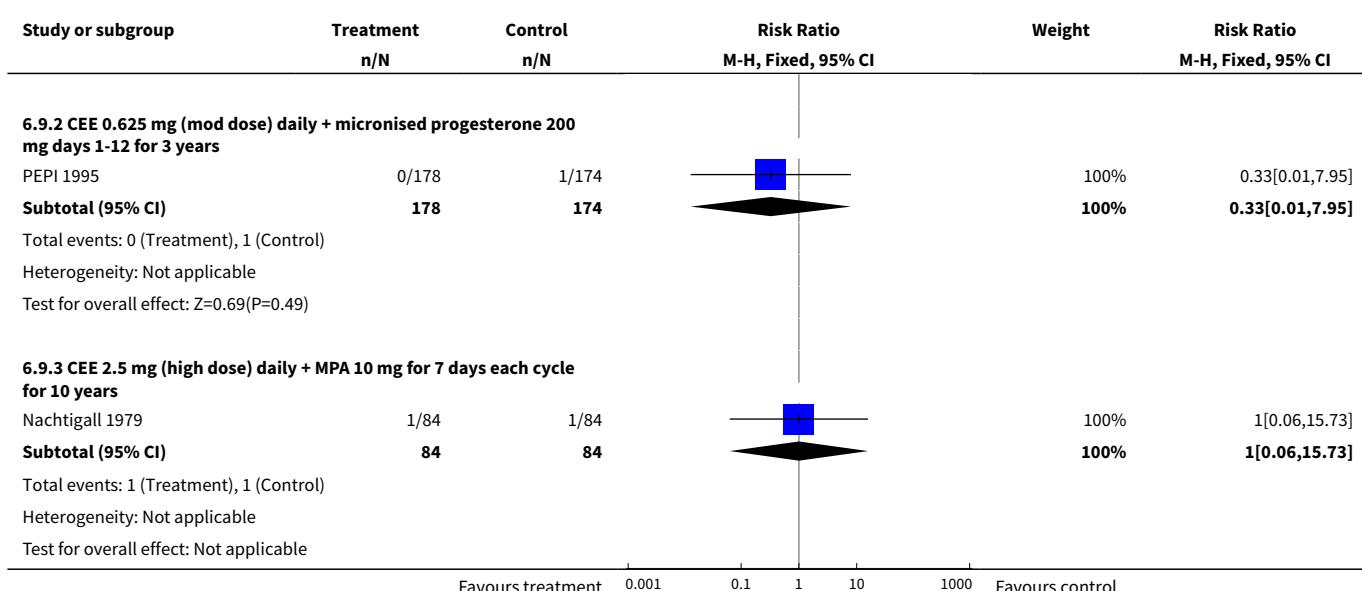
Analysis 6.8. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 8 Colorectal cancer: combined continuous HT.



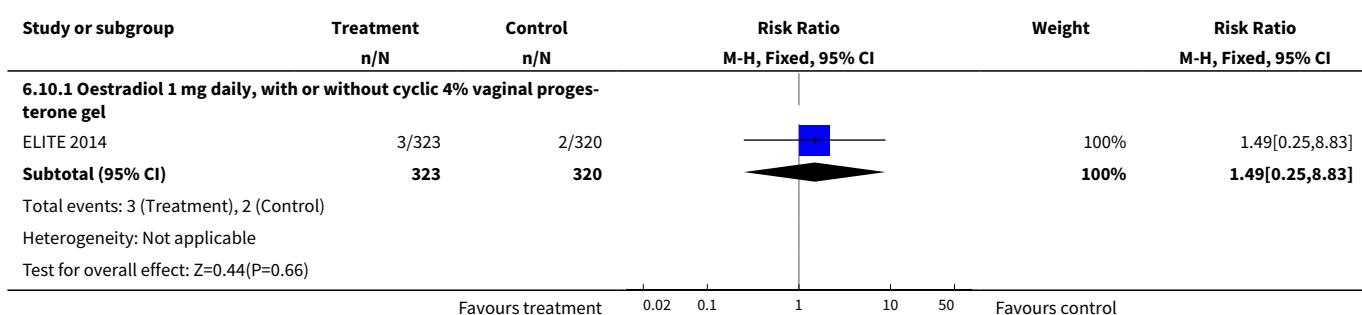


Analysis 6.9. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 9 Colorectal cancer: combined sequential HT.

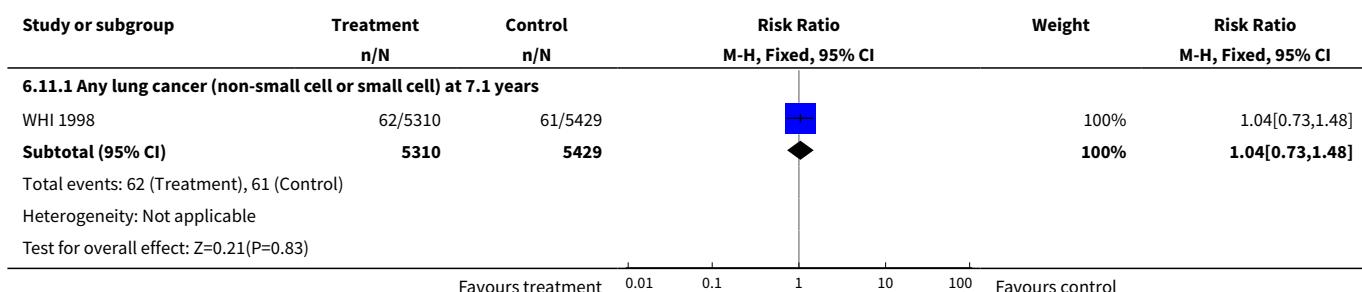




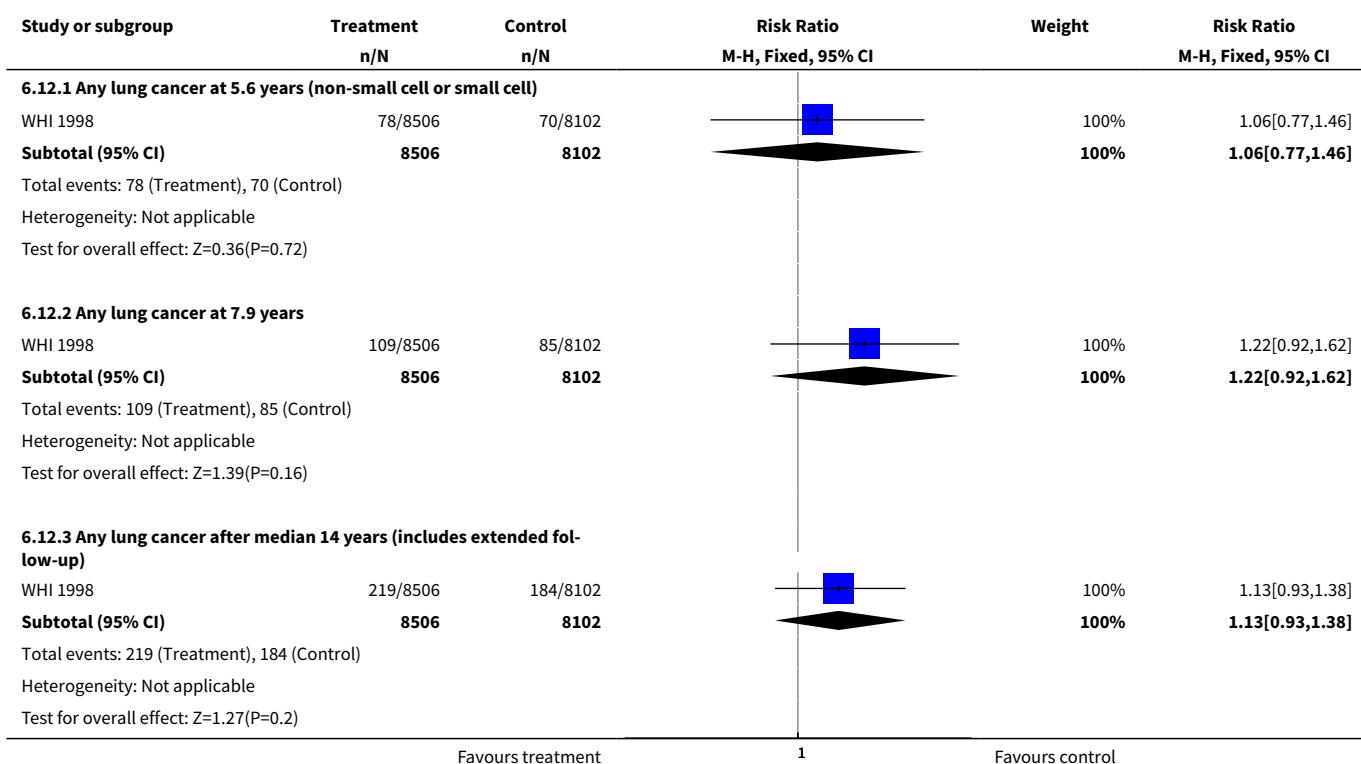
Analysis 6.10. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 10 Colorectal cancer: oestrogen with or without sequential progesterone vaginal gel.



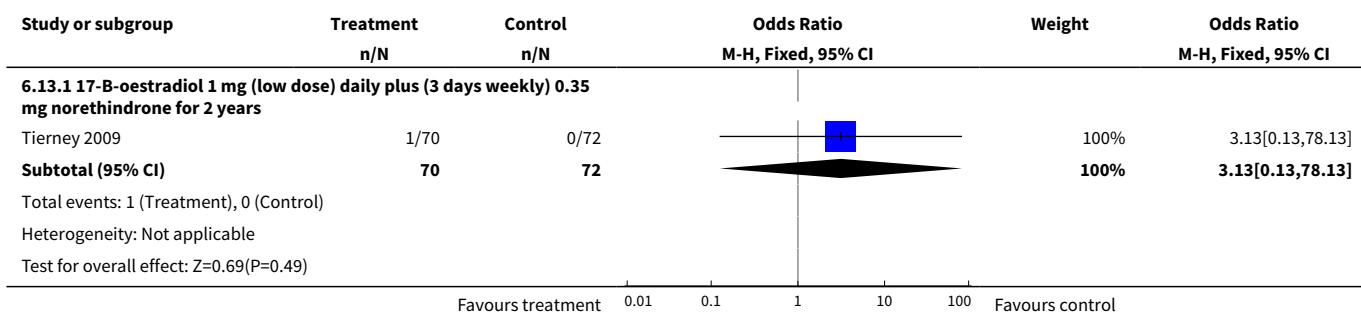
Analysis 6.11. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 11 Lung cancer: oestrogen-only HT (moderate dose).



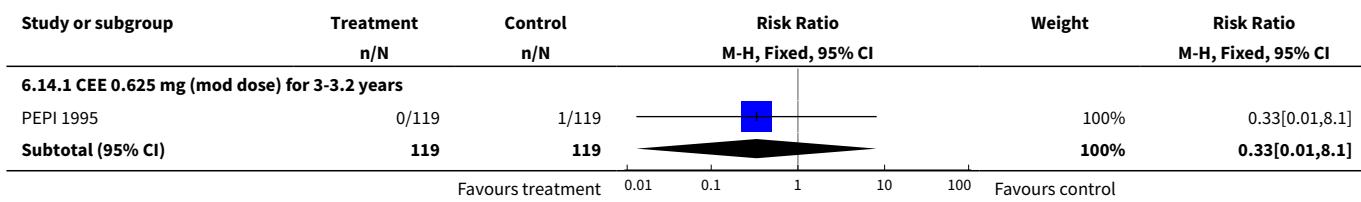
Analysis 6.12. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 12 Lung cancer: combined continuous HT (mod dose oestrogen).

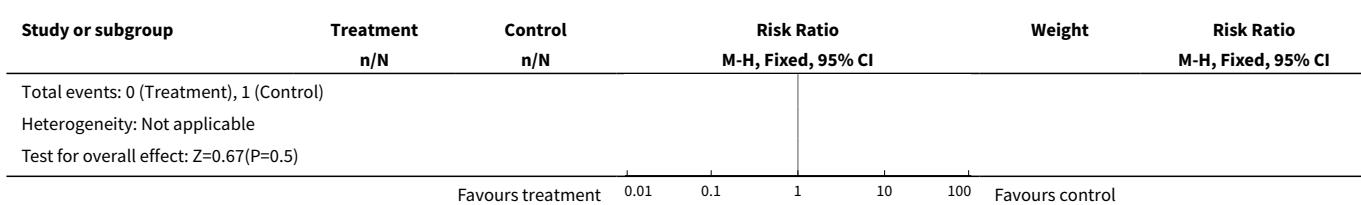


Analysis 6.13. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 13 Lung cancer: combined sequential HT.

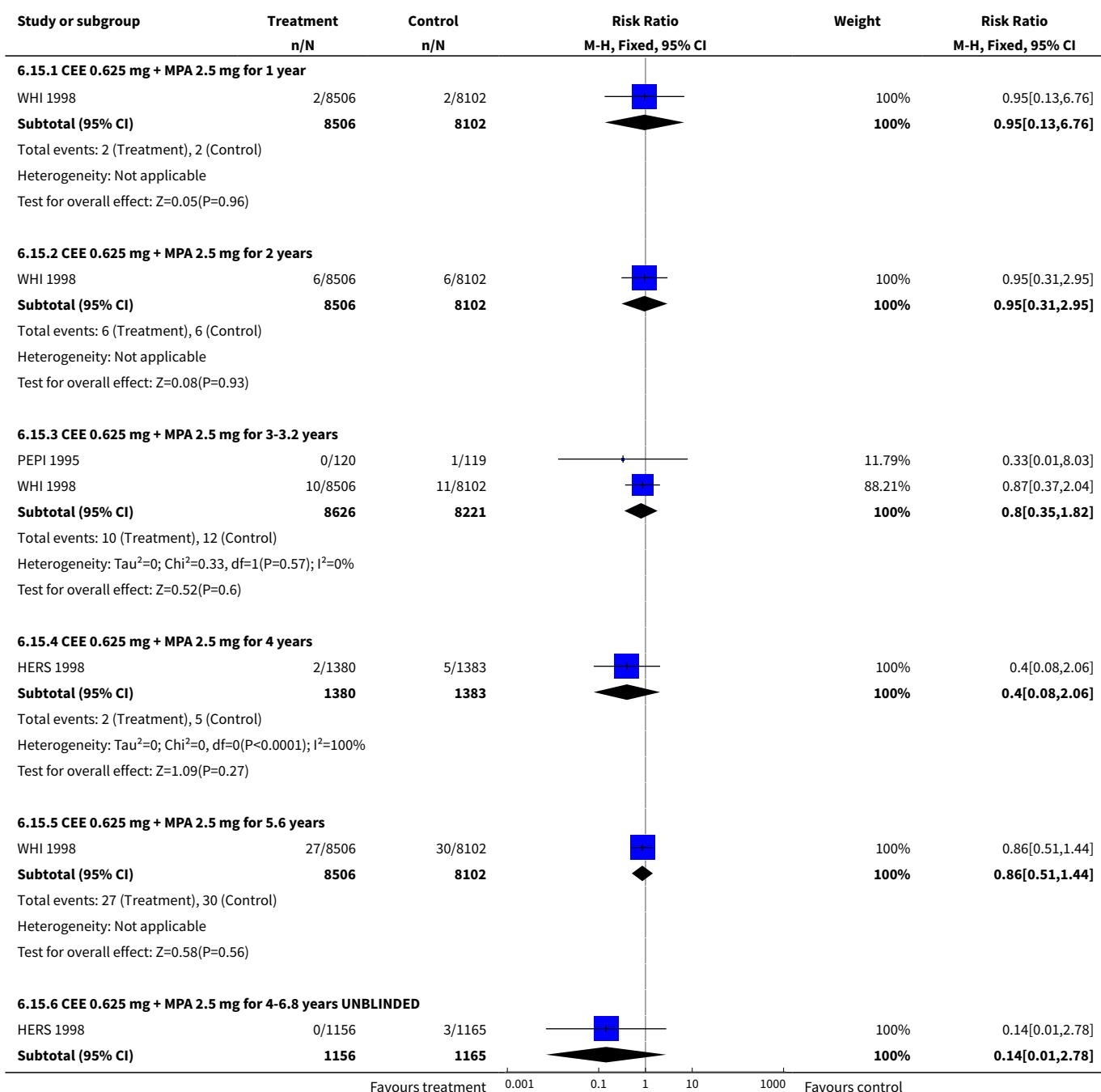


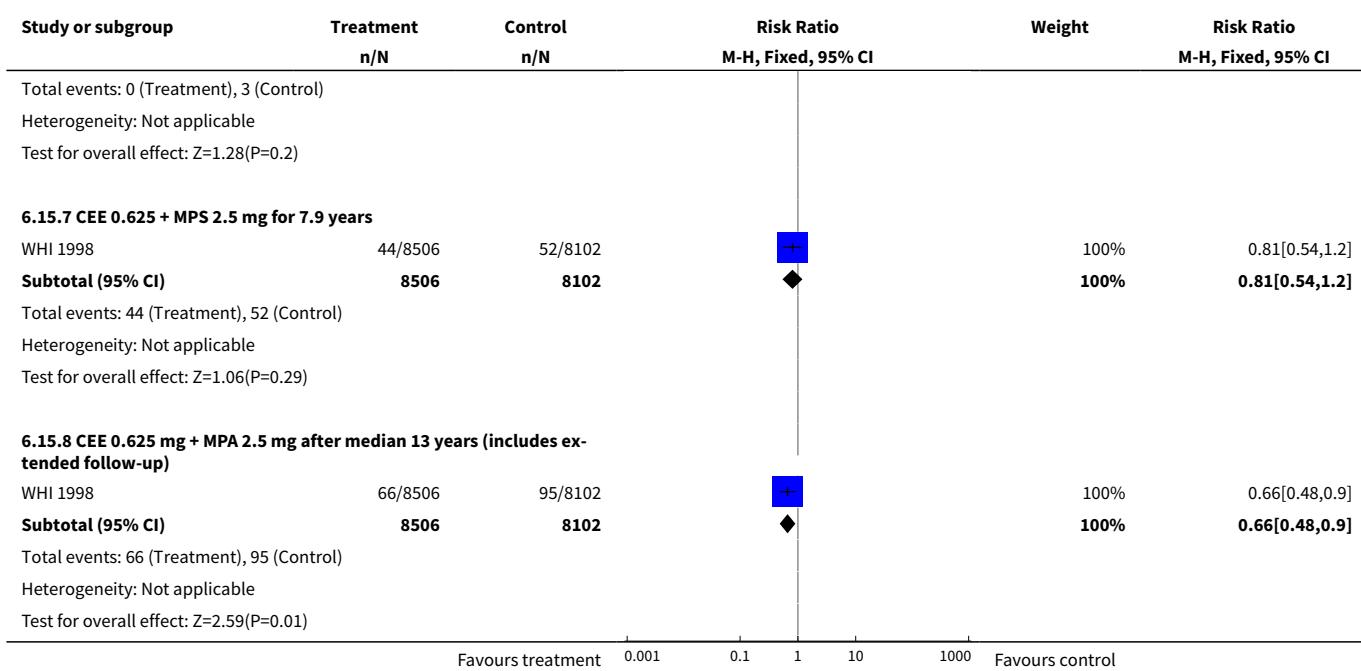
Analysis 6.14. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 14 Endometrial cancer: oestrogen-only HT.



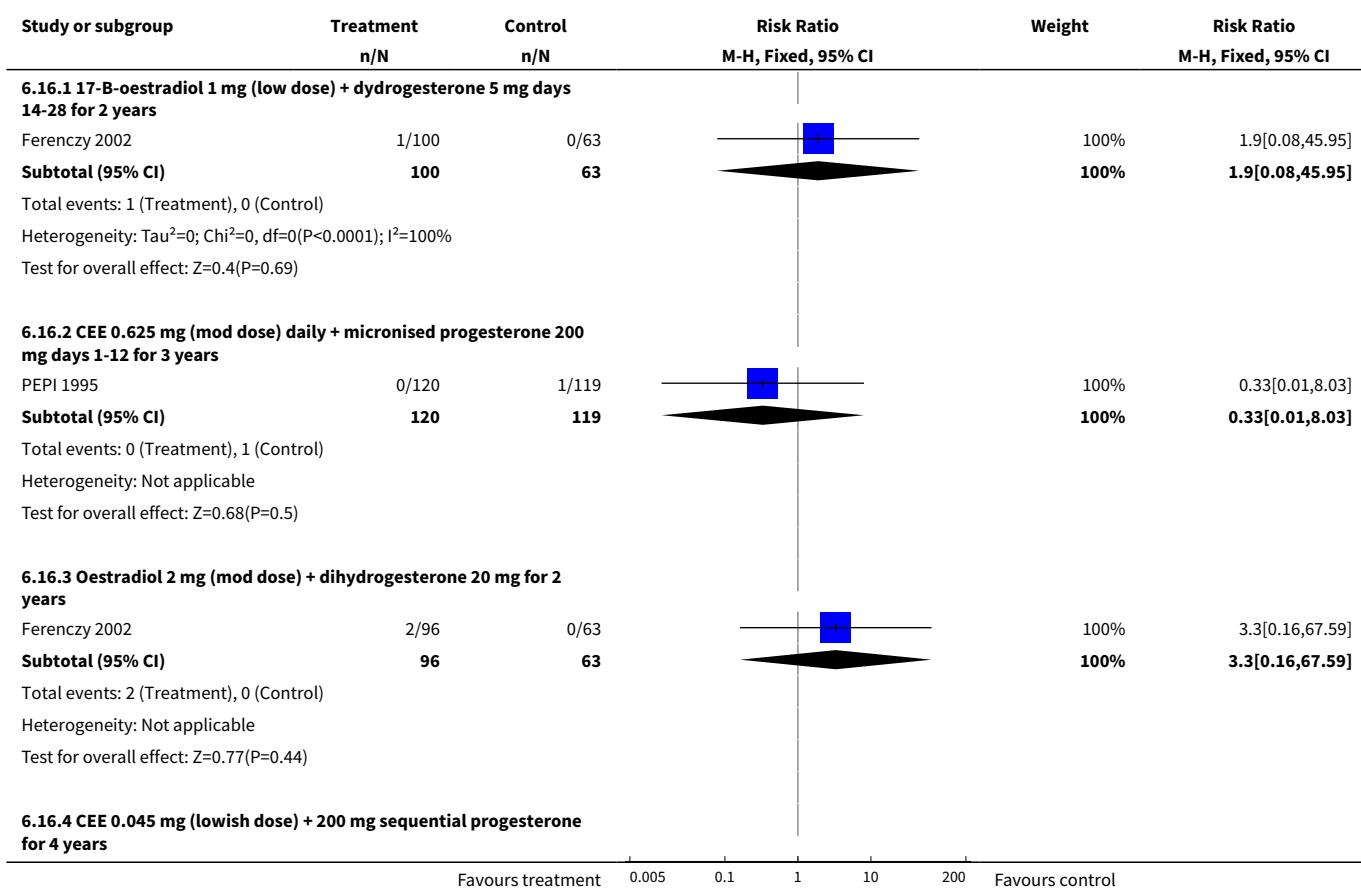


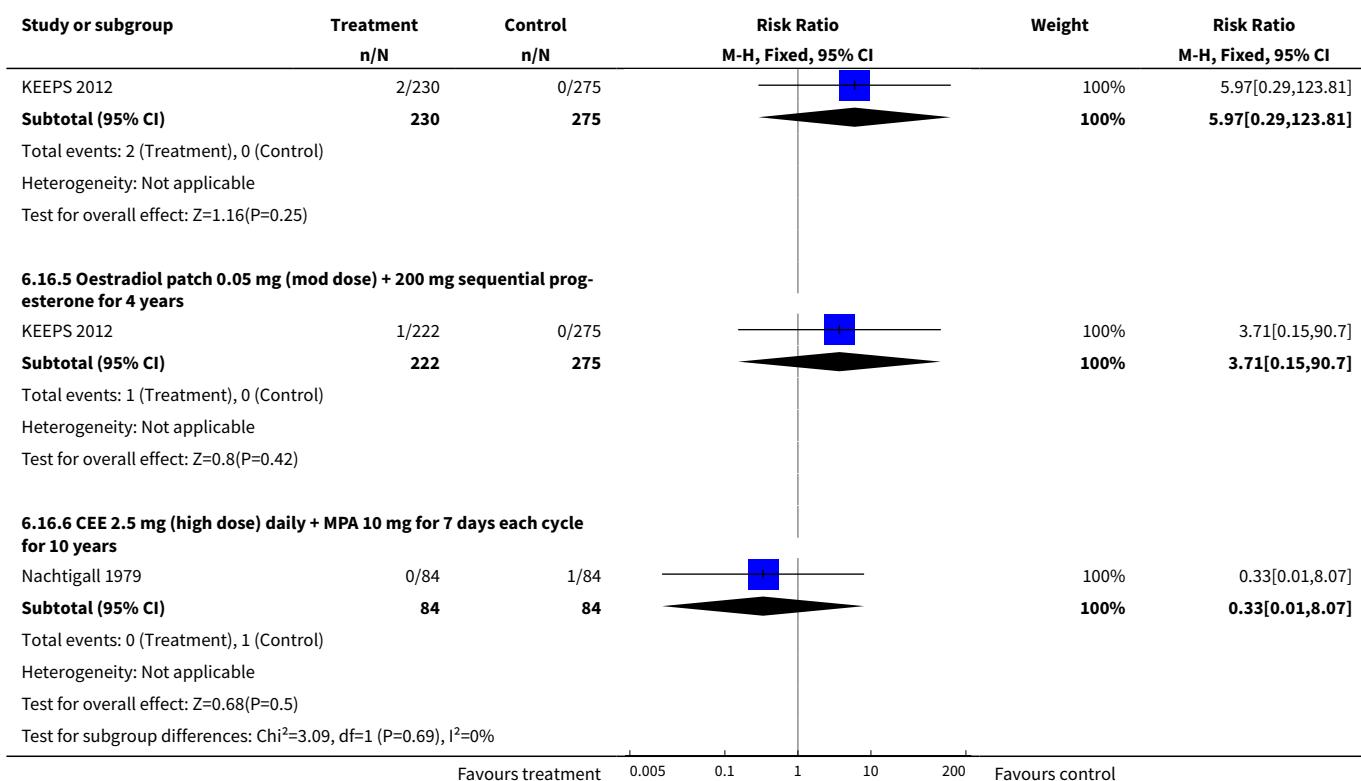
Analysis 6.15. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 15 Endometrial cancer: combined continuous HT (mode dose oestrogen).



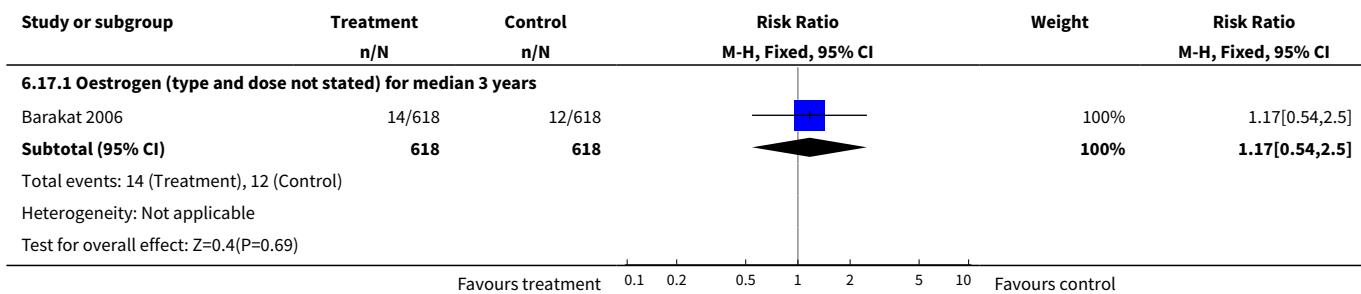


Analysis 6.16. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 16 Endometrial cancer: combined sequential HT.

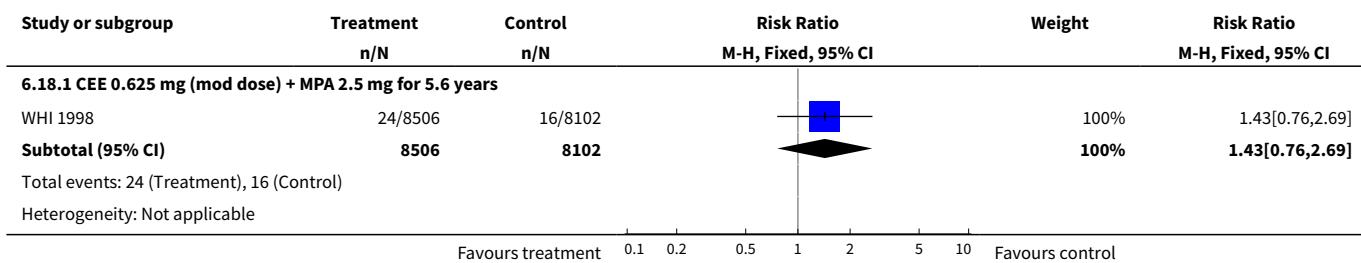


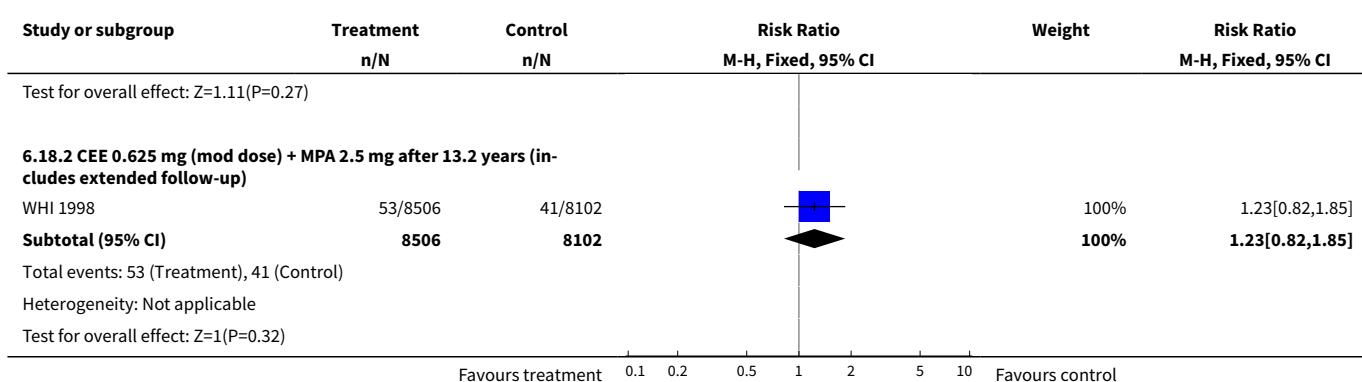


Analysis 6.17. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 17 Recurrent endometrial cancer: oestrogen-only HT.

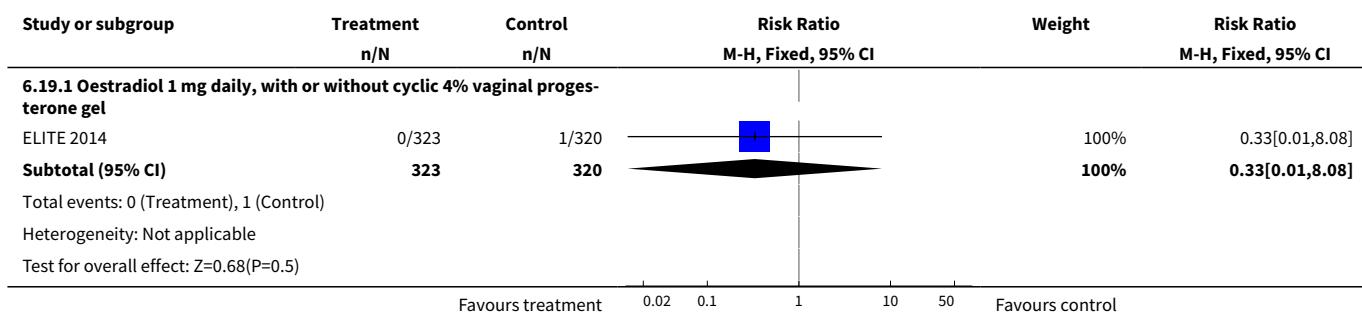


Analysis 6.18. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 18 Ovarian cancer: combined continuous HT.

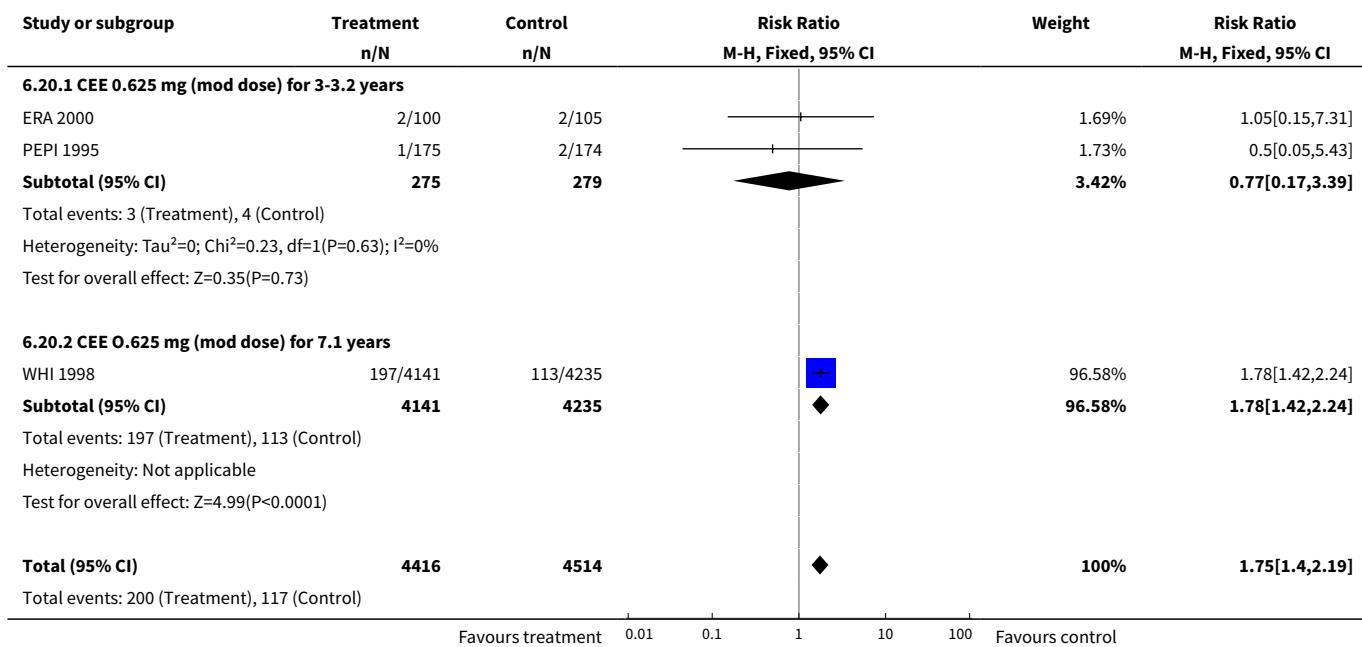


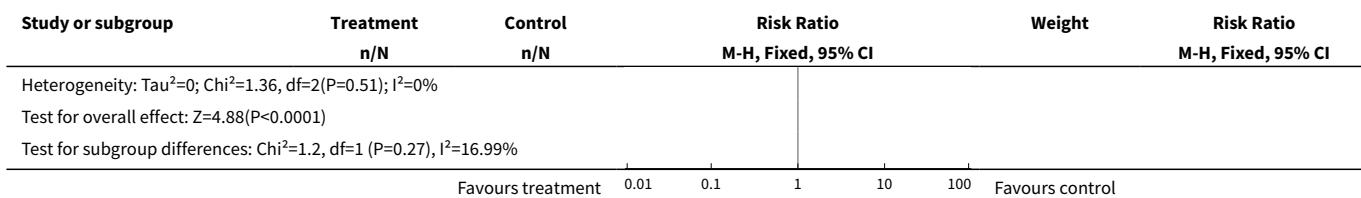


Analysis 6.19. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 19 Ovarian cancer: oestrogen with or without sequential progesterone vaginal gel.

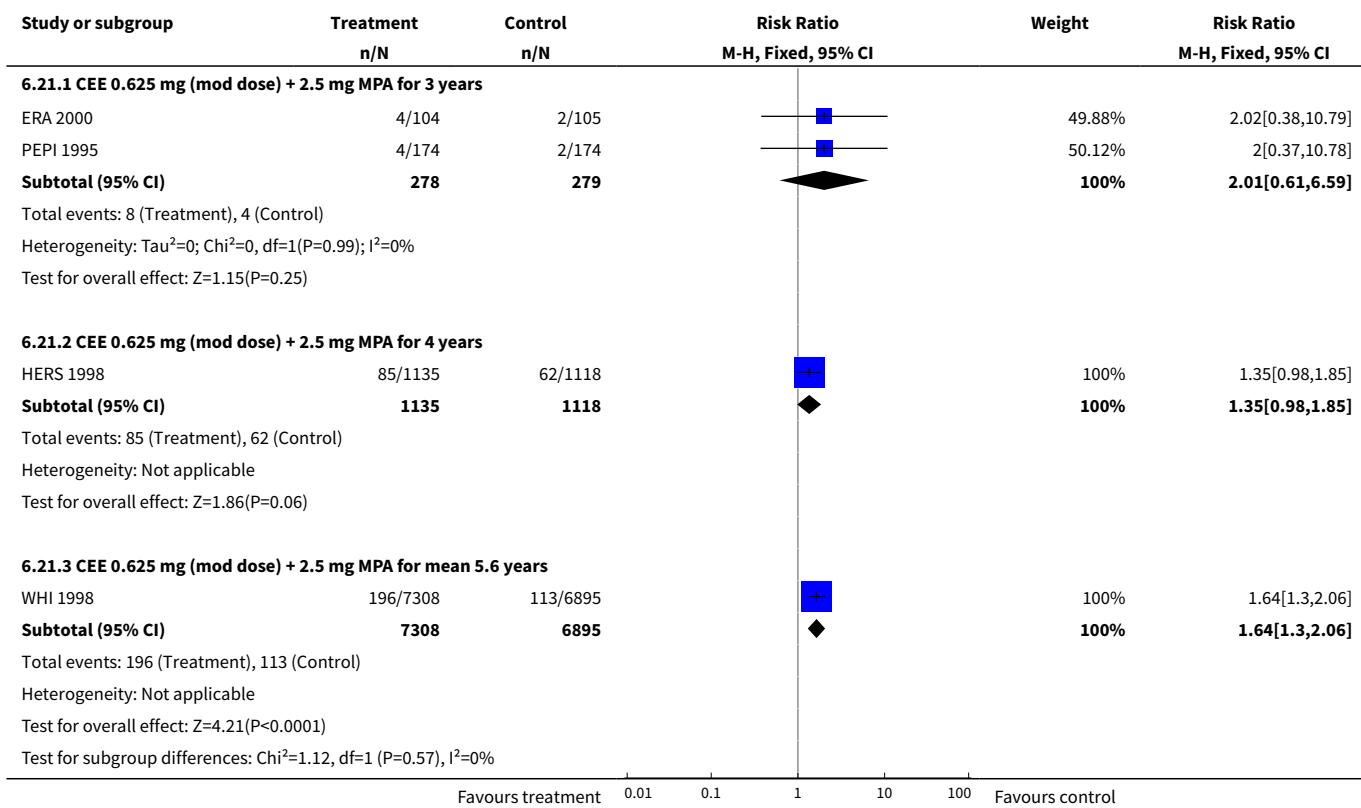


Analysis 6.20. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 20 Gallbladder disease requiring surgery: oestrogen-only HT.

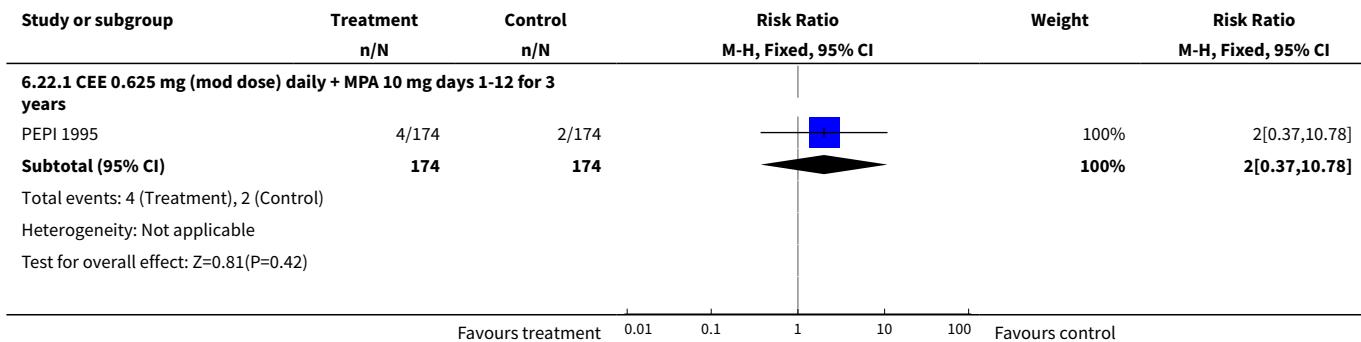


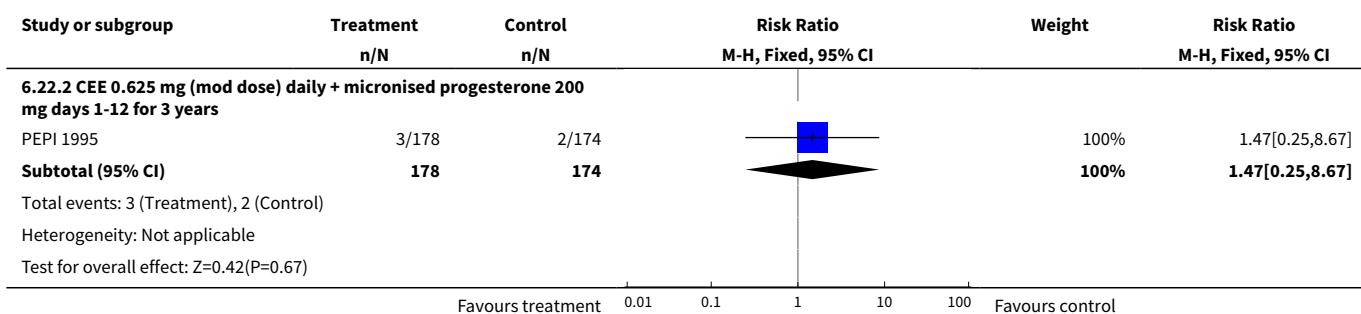


Analysis 6.21. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 21 Gallbladder disease requiring surgery: combined continuous HT.

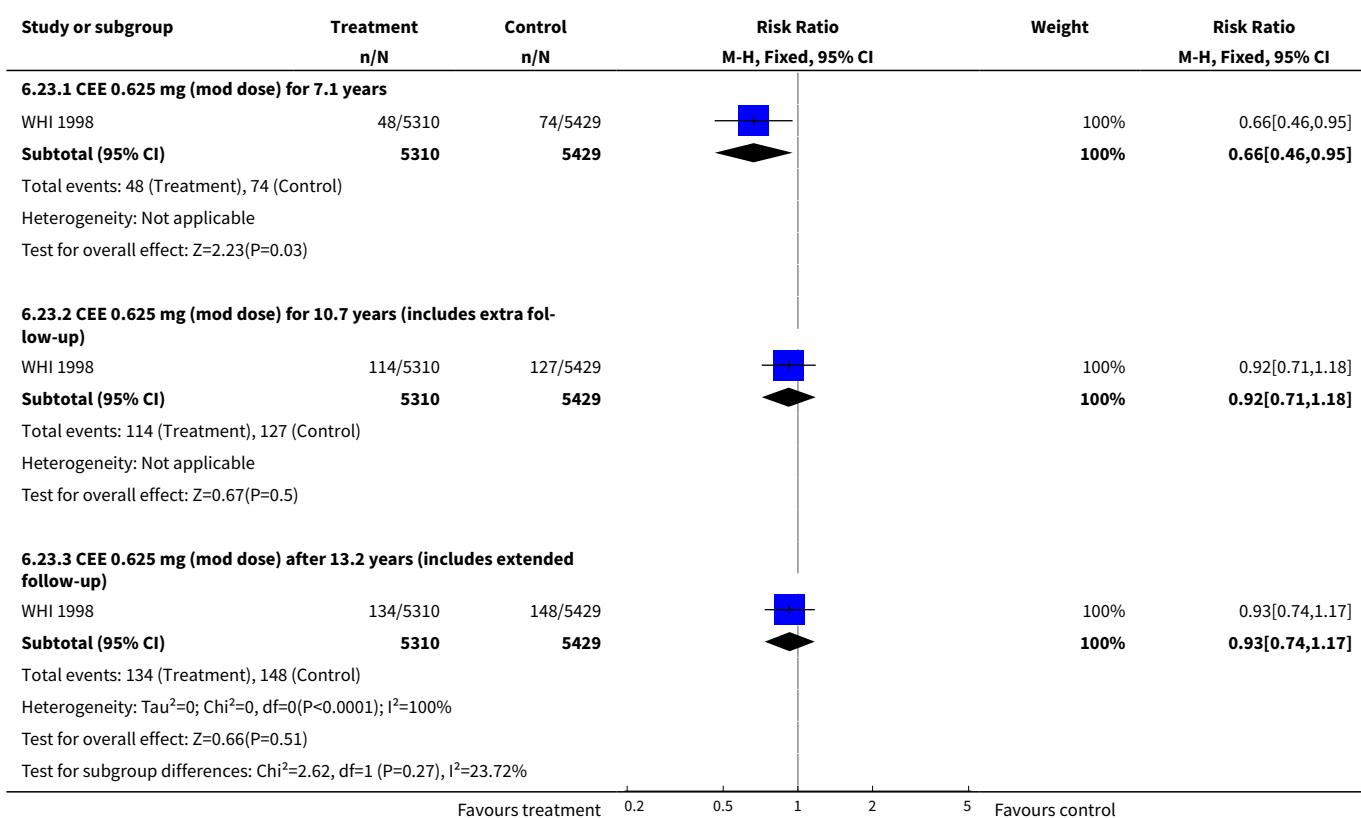


Analysis 6.22. Comparison 6 All women (selected outcomes: cancer, cholelithiasis, fractures), Outcome 22 Gallbladder disease requiring surgery: combined sequential HT.

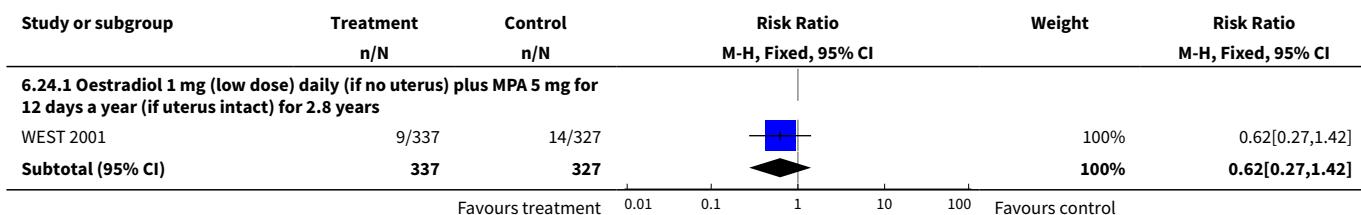


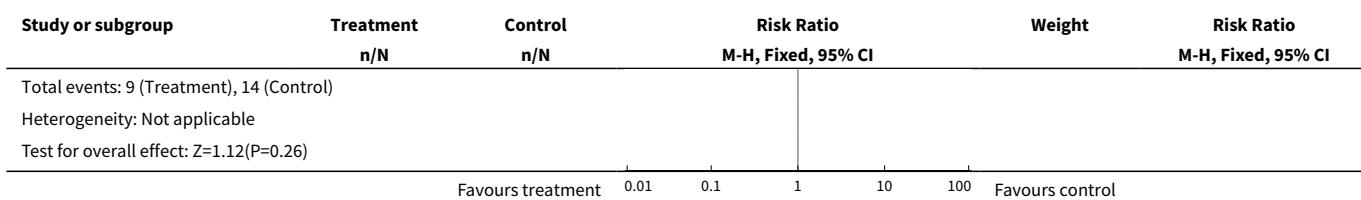


Analysis 6.23. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 23 Hip fractures: oestrogen-only HT.

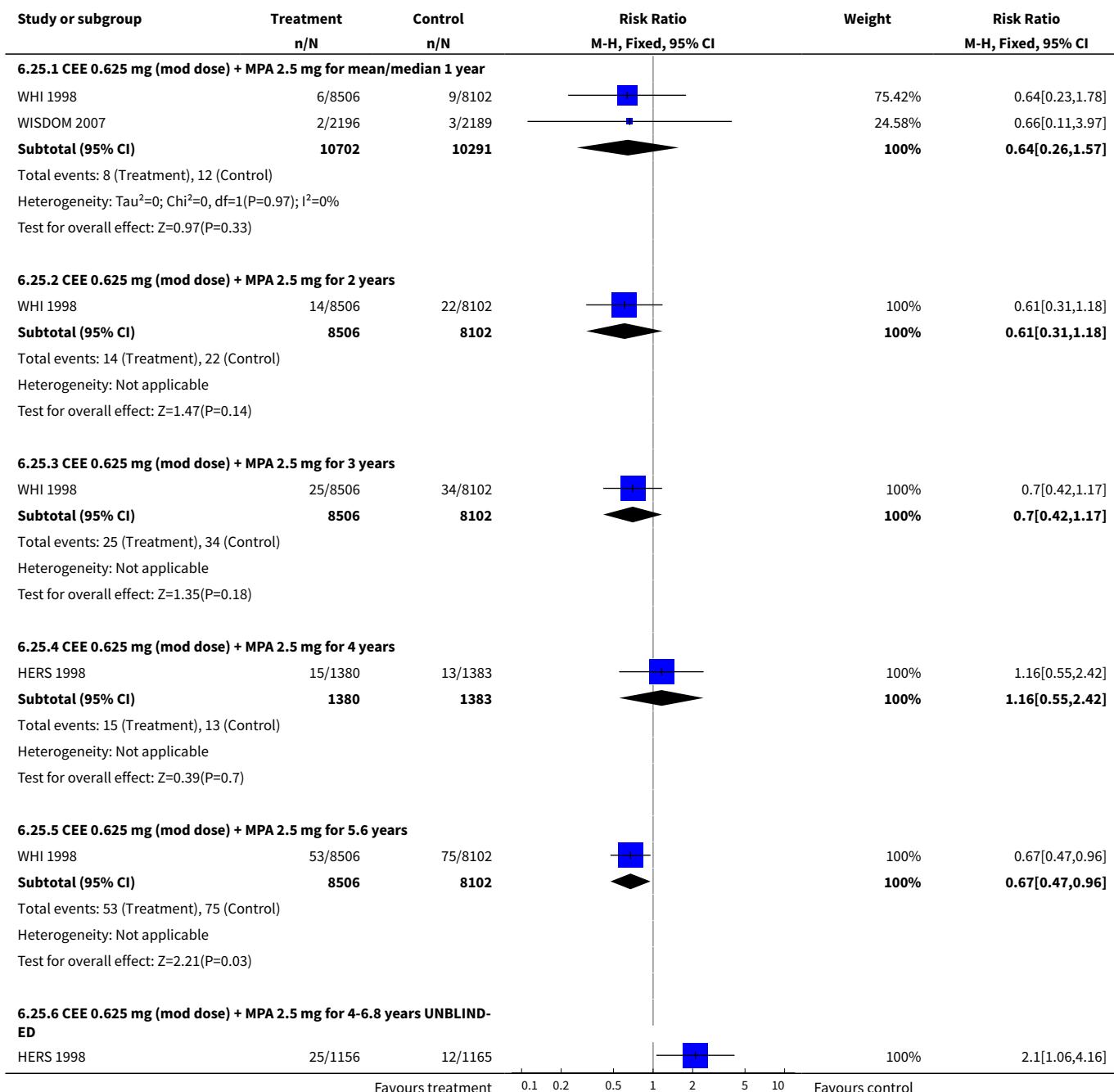


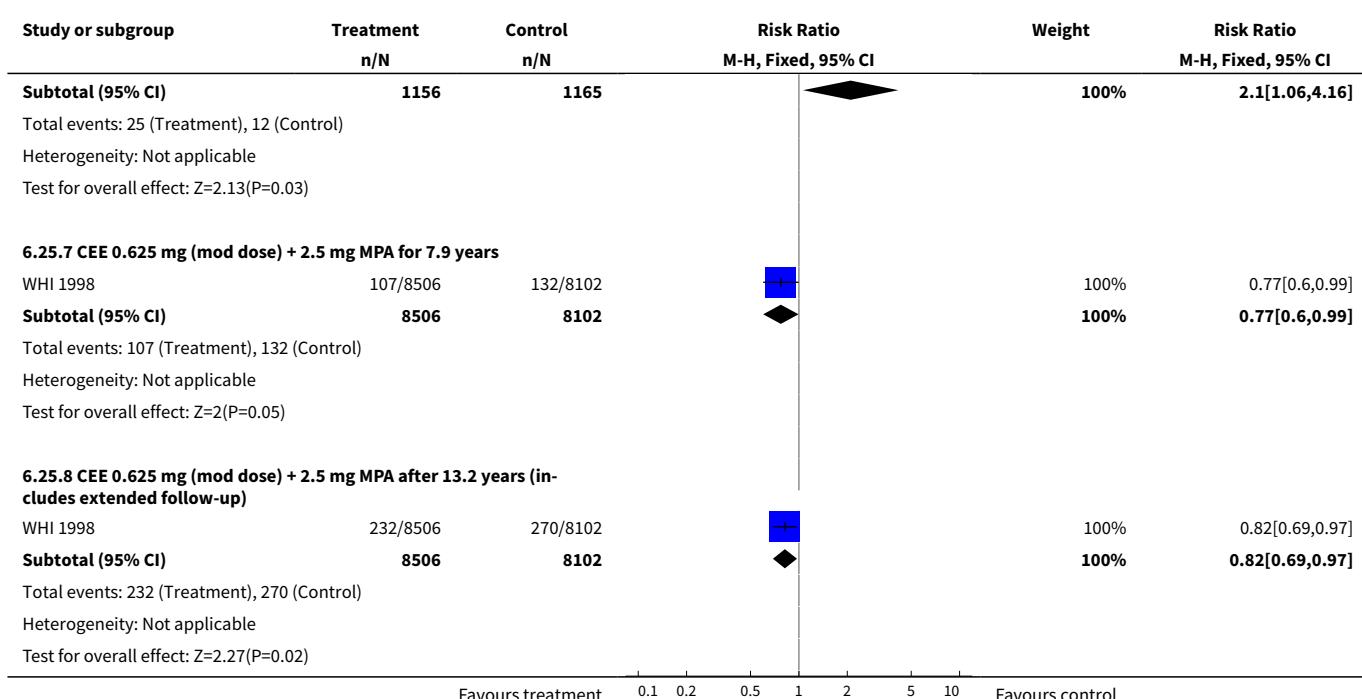
Analysis 6.24. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 24 Hip fractures: oestrogen-only or combined sequential HT.



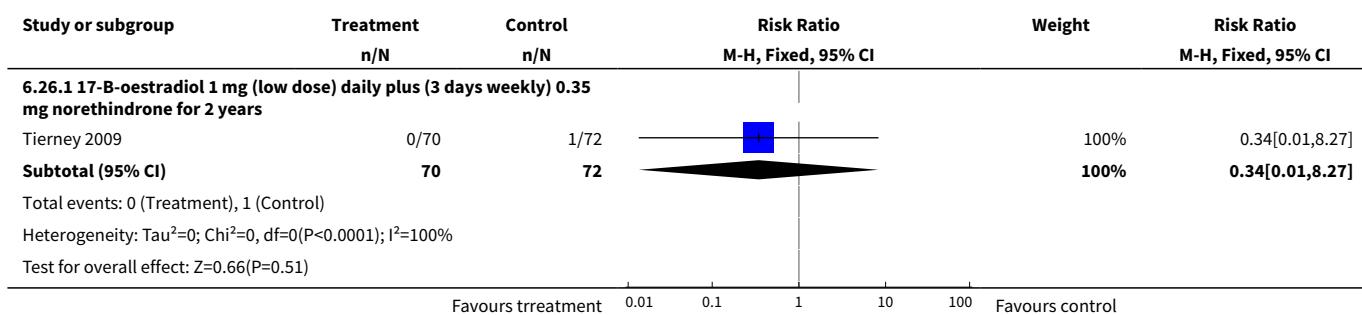


Analysis 6.25. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 25 Hip fractures: combined continuous HT.

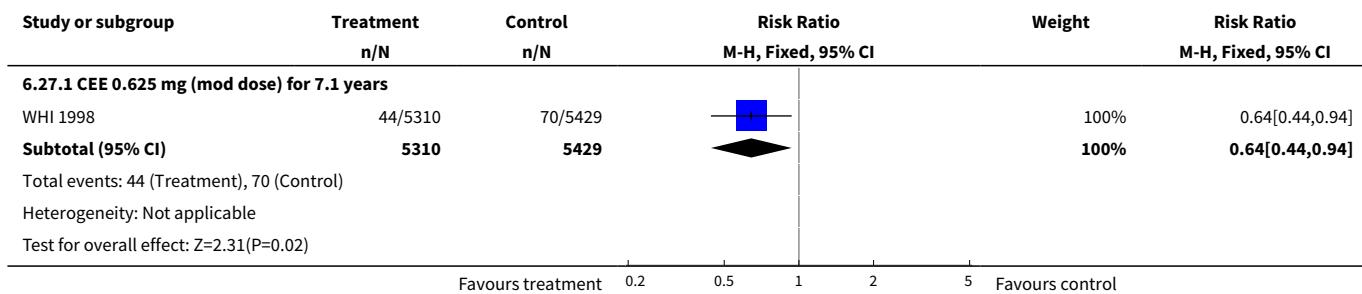




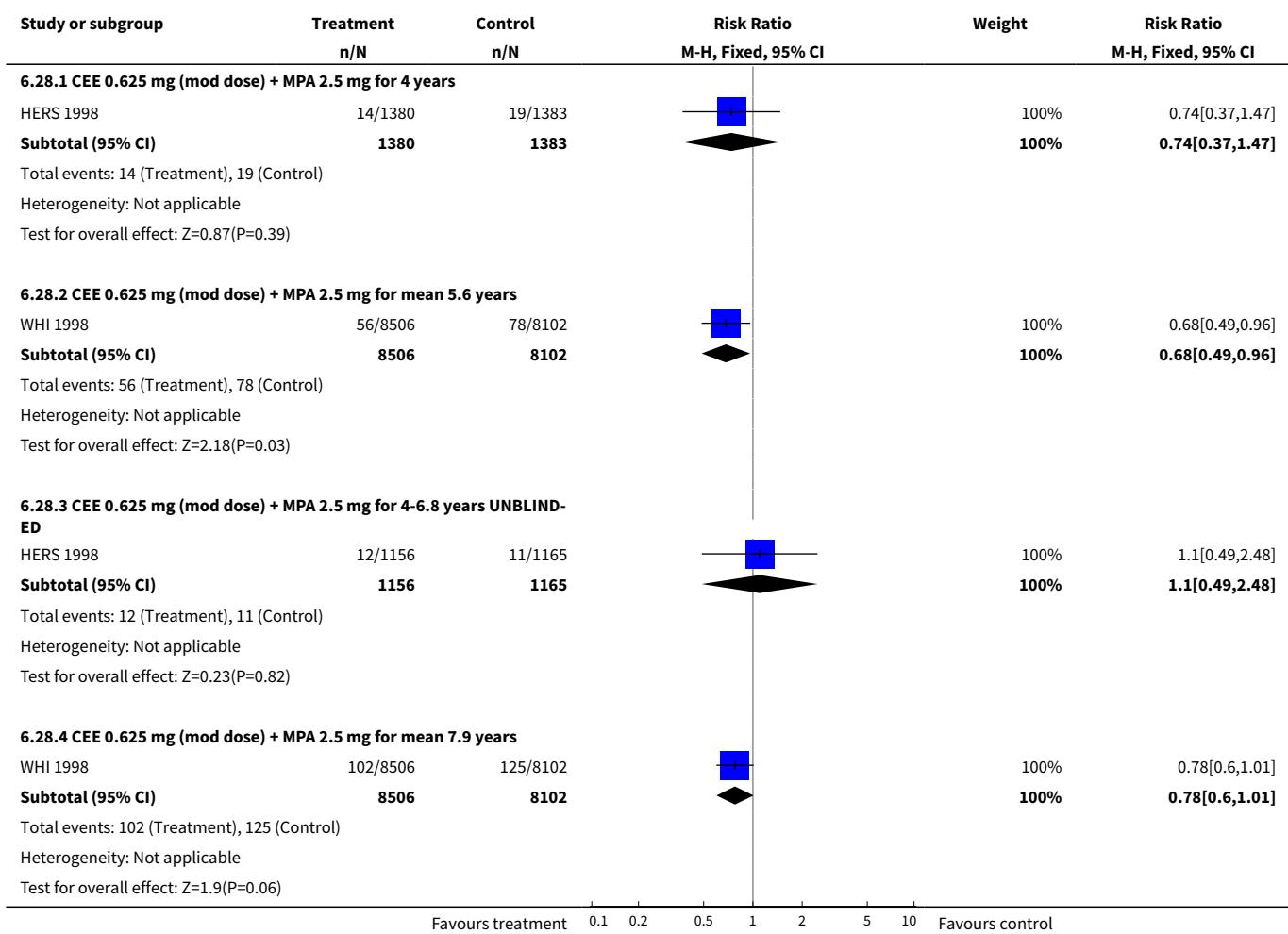
Analysis 6.26. Comparison 6 All women (selected outcomes: cancer, cholelithic disease, fractures), Outcome 26 Hip fractures: combined sequential HT.



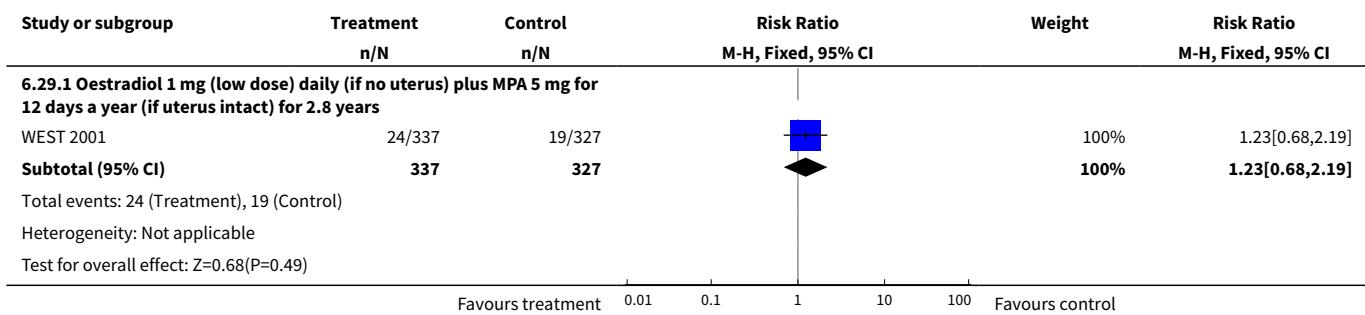
Analysis 6.27. Comparison 6 All women (selected outcomes: cancer, cholelithic disease, fractures), Outcome 27 Vertebral fractures: oestrogen-only HT.



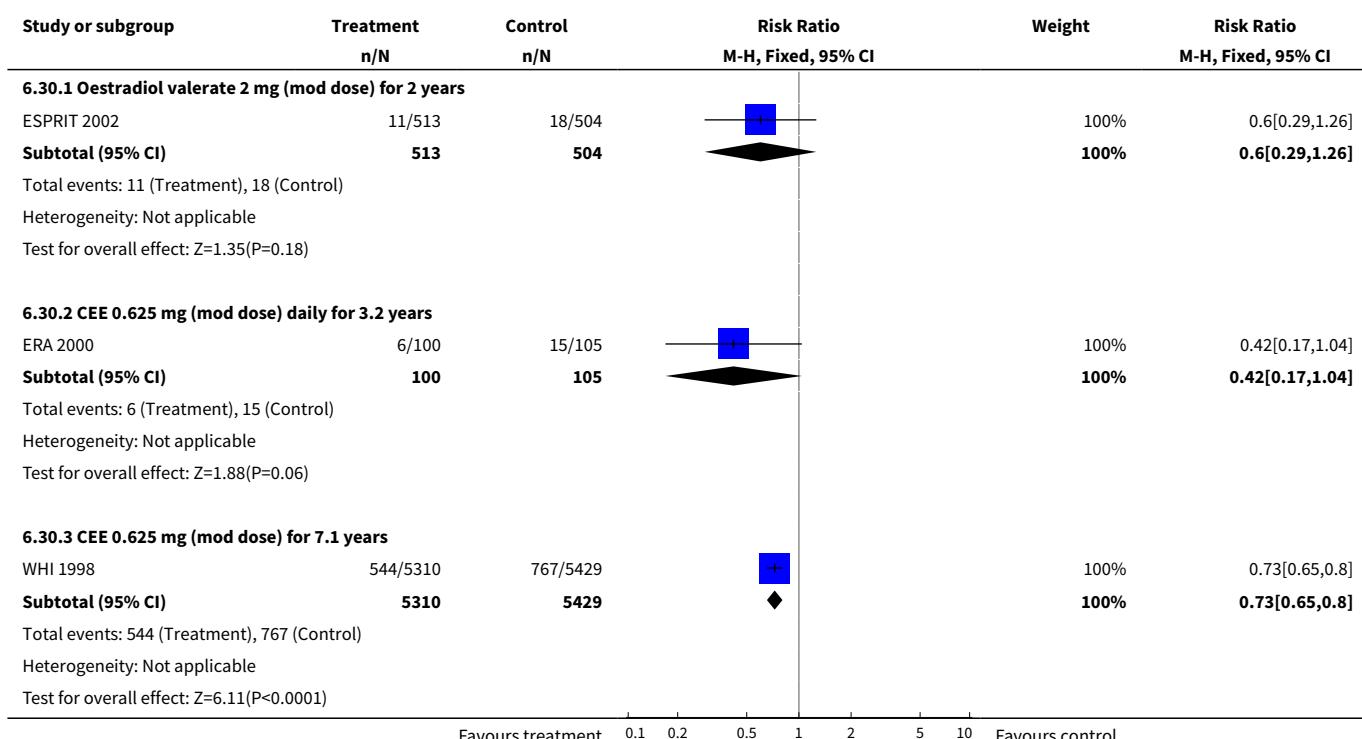
Analysis 6.28. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 28 Vertebral fractures: combined continuous HT.



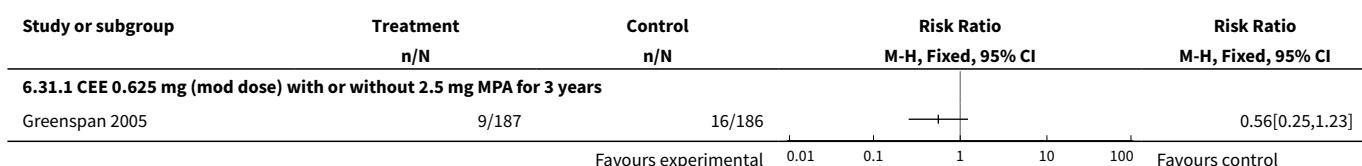
Analysis 6.29. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 29 All clinical fractures: oestrogen-only or combined sequential HT.



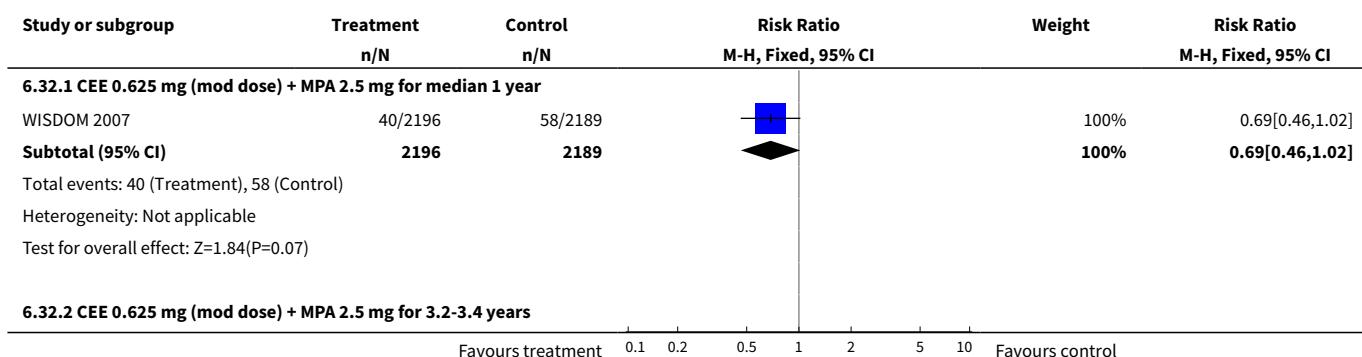
Analysis 6.30. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 30 All clinical fractures: oestrogen-only HT (moderate dose).

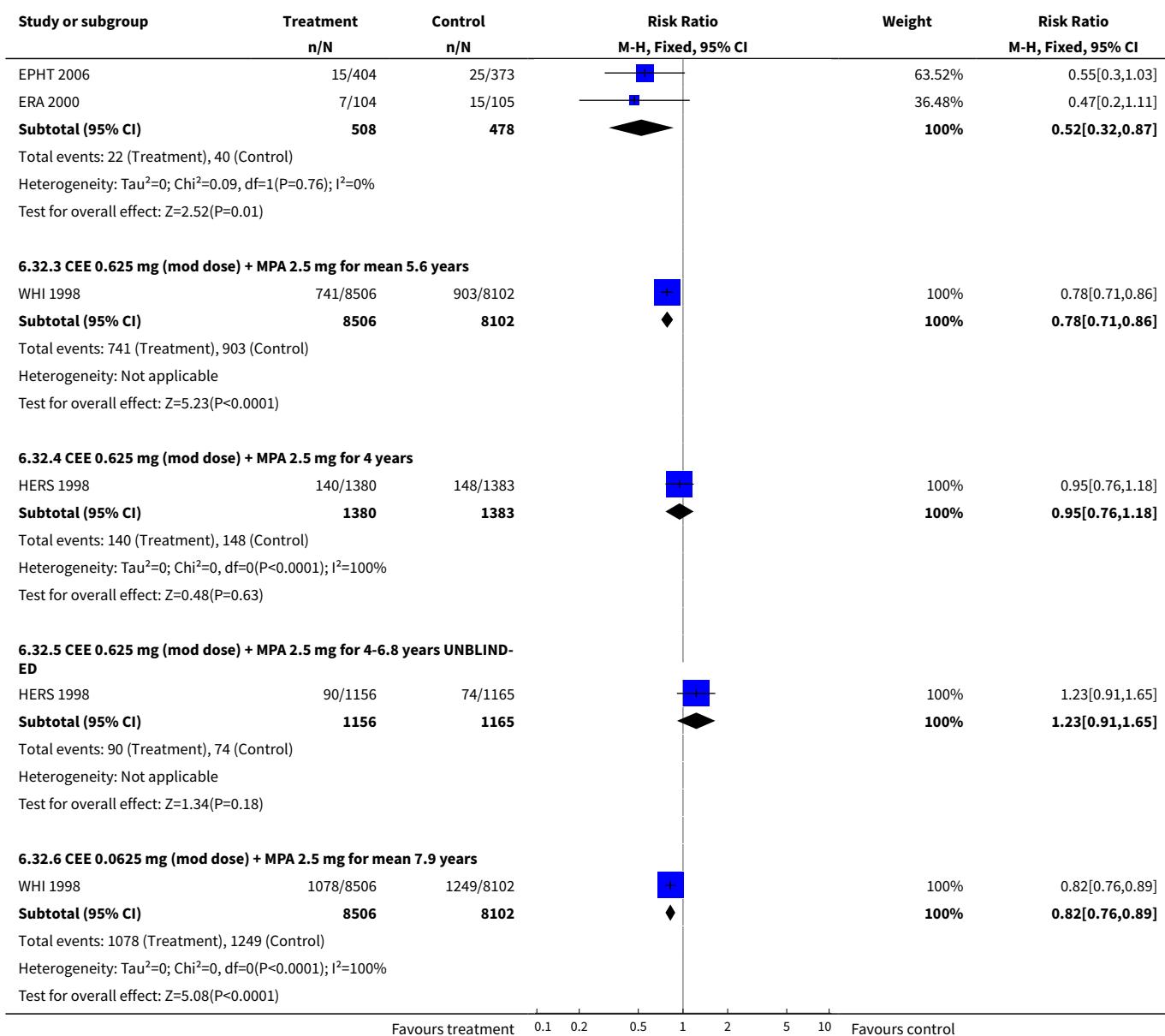


Analysis 6.31. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 31 All clinical fractures: oestrogen-only or combined HT.

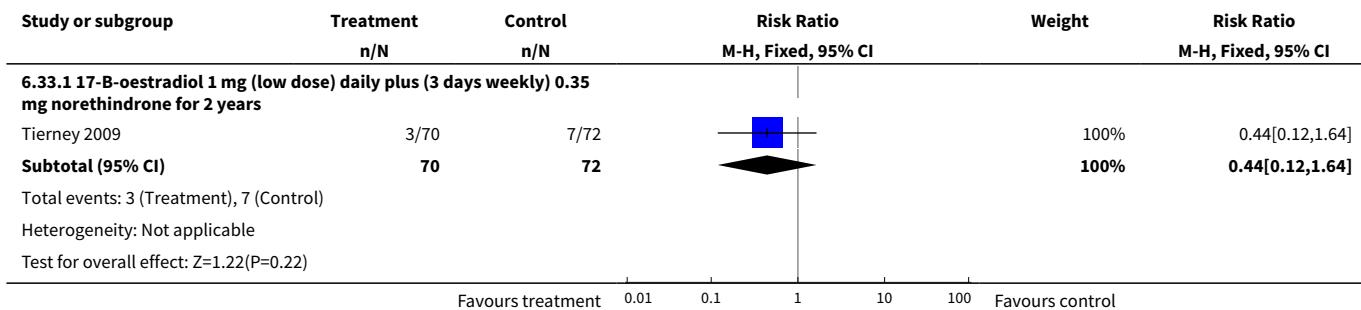


Analysis 6.32. Comparison 6 All women (selected outcomes: cancer, cholecystic disease, fractures), Outcome 32 All clinical fractures: combined continuous HT.





Analysis 6.33. Comparison 6 All women (selected outcomes: cancer, cholecytic disease, fractures), Outcome 33 All clinical fractures: combined sequential HT.



ADDITIONAL TABLES
Table 1. Adherence to treatment

Study	How defined	Assessment	HT group	Placebo group	Note
Barakat 2006	Discontinuation of therapy for longer than a month (or use of HT in placebo group)	Not stated	41.1% compliant for whole follow-up period (median 3 years)	50.1% compliant for whole follow-up period (median 3 years)	
ELITE 2014	> 80% of prescribed treatment taken	Pill counts	Median > 98% over median of 5 years	Median > 98% over median of 5 years	
EPAT 2001	Percentage of study medication consumed	Pill counts	Level of adherence 95% in the 87% of participants evaluated	Level of adherence 92% in the 92% of participants evaluated	
EPHT 2006	> 80% of prescribed treatment taken	Number of collected and returned drugs and clinic reports	< 40% compliant at 3 years (estimated from graph)	< 30% compliant at 3 years (estimated from graph)	
ERA 2000	Percentage of study medication taken	Pill counts	Level of adherence at 3.2 years: Women on unopposed oestrogen, measured in 79% of participants only: 74%	Level of adherence at 3.2 years: Measured in 80% of participants only: 86%	
			Women on combined HRT, measured in 82% of participants only: 84%	5 women initiated treatment outside study	
ESPRIT 2002	"Regular tablet use"	Self-report to family doctor. Self-report to study nurse at 6 weeks and whenever in contact with trial staff	Number non-adherent: 51% at 12 months 57% at 24 months	Number non-adherent: 31% at 12 months 337% at 24 months	Triallists attribute higher non-compliance in HRT group to prevalence of vaginal bleeding (reported by 56% in HRT group, 7% in controls)
EVTET 2000	Adherence not described				
Ferenczy 2002	Adherence not described				
Greenspan 2005	"Taking at least 80% of medication	Pill counts 6-monthly	90% adherent at 3 years	94% adherent at 3 years	

Table 1. Adherence to treatment (Continued)

 for at least 80% of
 entire study period^a

HERS 1998	Taking at least 80% of study medication	Pill counts	79% adherent at 1 year 70% adherent at 3 years 3% initiated treatment outside study About 50% continued to use open-label HRT during unblinded follow up (4.2-6.8 years)	91% adherent at 1 year 81% non-adherent at 3 years Less than 10% used HRT during unblinded follow-up (4.2-6.8 years)	Proportion of women who reported taking study medication at 1 year: HRT group: 82% Placebo group: 91%
KEEPS 2012	Pill or patch counts, percentage used	Pill counts or weights	94%-95% in all groups, among women who completed trial at 4 years		
Mulnard 2000	Taking at least 80% of study medication	Plasma oestradiol level evaluation at each visit Pill counts at each visit	No information given in publication		
Nachtigall 1979	Adherence not described				
Notelovitz 2002	Adherence not described				
Obel 1993	Adherence not described				
PEPI 1995	Taking at least 80% of study medication	Study diary reviewed at clinic visits Pill counts	Number adherent at 36 months: Women without uterus: 80%-89% at 36 months Women with uterus: 1. On unopposed CEE: 44% 2. On combined therapy: 80%	Number adherent at 36 months: Women without uterus: 67% Women with uterus: 76%	
Tierney 2009	Taking at least 80% of study medication	Pill counts weekly	No information given in publication		
WAVE 2002	Percentage of study medication taken	Pill counts	At 2.8 years: Adherence 67% in the 78% of women analysed	At 2.8 years: Adherence 70% in the 81% of women analysed	
WEST 2001	Percentage of study medication taken	Self-report to study nurse 3-monthly Computer chip in medication bottle records opening date and time	At 2.8 years: Mean adherence including drop-outs: 70% Mean adherence excluding dropouts: 90%	At 2.8 years: Mean adherence including dropouts: 74% over 2.8 years Mean adherence excluding dropouts: 90%	

Table 1. Adherence to treatment (Continued)

	Pill counts	35% discontinued medication by 2.8 years, of whom 1% initiated treatment outside study	24% discontinued medication 2% initiated treatment outside study
WHI 1998 (unopposed oestrogen arm)	Taking at least 80% of study medication. Temporary discontinuation (e.g. during surgery) permitted	Weighing of returned medication bottles	At 6.8 years, about 53.8% of women were non-adherent In addition, 5.7% of women had initiated hormone use through their own physician
WHI 1998 (combined arm)	Taking at least 80% of study medication. Temporary discontinuation (e.g. during surgery) permitted	Weighing of returned medication bottles	At 6.8 years, about 53.8% of women were non-adherent In addition 9.1% of women had initiated hormone use through their own physician
WISDOM 2007	Supply of study medication	Time at risk minus temporary interruptions and time after withdrawal from treatment	42% non-adherent by 5.2 years Of these, 6.2% initiated HRT outside study
Yaffe 2006	Supply of study medication	Patch counts: 75% use over 2 years counted as compliance	84% of time 84% of time
			Analyses censoring events 6 months after non-adherence increased effect sizes
			Women had a 3 month run-in period on placebo. Only women who took 80% of tablets were randomised
			Women had a 1 week run-in period.
			Only compliant women were randomised.

Table 2. Other data

Study	Comparison	Instrument	Measure	Outcome	Intervention	Effect
KEEPS 2012	Oestrogen (CEE or oestradiol) + cyclic oral micronised progesterone 200 mg/d × 12 days per month vs placebo (n = 275) for 48 months	Modified Mini Mental State Examination (MMSE)	Differences between intervention and placebo groups in mean rate of change over time	Global cognition	0.45 mg/d oral CEE (n = 230) 0.05 mg/d transdermal oestradiol (n = 222)	P = 0.178 P = 0.840

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group Specialised Register search strategy

From inception to 5th September 2016

PROCITE platform

Keywords CONTAINS "menopausal" or "Menopause" or "menopause-surgical" or "perimenopausal" or "perimenopause" or "postmenopausal" or "postmenopause" or "climacteric" or Title CONTAINS "menopausal" or "menopause-surgical" or "perimenopausal" or "perimenopause" or "postmenopausal" or "postmenopause" or "climacteric" or "Menopause"

AND

Keywords CONTAINS "HRT" or "HT" or "hormone replacement therapy" or "Hormone Substitution" or "hormone therapy" or "progestagen" or "Progesterone" or "progesterin" or "progestins" or "progesterogen" or "progestogens" or "medroxyprogesterone" or "MPA" or "dydrogesterone" or "dydrogestrone" or "*Estradiol" or "Estriol-" or "estrogen" or "**Estrogens" or "oestradiol" or "oestrogen" or "CEE" or "CEE + MPA" or "conjugated equine" or "premarin" or "17-beta estradiol" or "17beta-estradiol + norethisterone acetate" or Title CONTAINS "HRT" or "HT" or "hormone replacement therapy" or "Hormone Substitution" or "hormone therapy" or "progestagen" or "Progesterone" or "progesterin" or "progestins" or "progesterogen" or "progestogens" or "medroxyprogesterone" or "MPA" or "dydrogesterone" or "dydrogestrone" or "*Estradiol" or "Estriol-" or "estrogen" or "**Estrogens" or "oestradiol" or "oestrogen" or "CEE" or "CEE + MPA" or "conjugated equine" or "premarin" or "17-beta estradiol" or "17beta-estradiol + norethisterone acetate"

(3443 hits)

Appendix 2. CENTRAL search strategy

From inception to 5th September 2016

CRSO web platform

```
#1 MESH DESCRIPTOR Climacteric EXPLODE ALL TREES (6208)
#2 MESH DESCRIPTOR Menopause EXPLODE ALL TREES (5986)
#3 MESH DESCRIPTOR perimenopause EXPLODE ALL TREES (92)
#4 MESH DESCRIPTOR Postmenopause EXPLODE ALL TREES (4016)
#5 MESH DESCRIPTOR Hot Flashes EXPLODE ALL TREES (571)
#6 (postmenopaus* or post-menopaus* or post menopaus*):TI,AB,KY (12065)
#7 (perimenopaus* or peri-menopaus* or peri menopaus*):TI,AB,KY (512)
#8 (climacter* or menopaus*):TI,AB,KY (6621)
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 (15564)
#10 MESH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES (2716)
#11 (HT or HRT):TI,AB,KY (3774)
#12 MESH DESCRIPTOR Progestins EXPLODE ALL TREES (1959)
#13 progesterogen*:TI,AB,KY (675)
#14 progesterone:TI,AB,KY (4345)
#15 (medroxyprogesterone acetate or MPA):TI,AB,KY (2402)
#16 dydrogesterone:TI,AB,KY (221)
#17 (norethisterone or norethindrone):TI,AB,KY (1053)
#18 (hormone adj1 therap*):TI,AB,KY (4934)
#19 (estrogen* or oestrogen*):TI,AB,KY (9441)
#20 estradiol:TI,AB,KY (7032)
#21 CEE:TI,AB,KY (332)
#22 (conjugated equine estrogen*):TI,AB,KY (585)
#23 premarin:TI,AB,KY (165)
#24 estriol:TI,AB,KY (329)
#25 oestradiol:TI,AB,KY (1022)
#26 (mestranol or estrone):TI,AB,KY (761)
#27 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 (21577)
#28 #9 AND #2777 (23)
```

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946 to 5th September 2016

Ovid platform

- 1 exp climacteric/ or exp menopause/ or exp perimenopause/ or exp postmenopause/ (54052)
- 2 (postmenopaus\$ or post-menopaus\$ or post menopaus\$).tw. (53161)
- 3 (perimenopaus\$ or peri-menopaus\$ or peri menopaus\$).tw. (3986)
- 4 (climacter\$ or menopaus\$).tw. (44202)
- 5 or/1-4 (94884)
- 6 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (22896)
- 7 HT.tw. (56334)
- 8 exp Progestins/ (64617)
- 9 progestogen.tw. (3549)
- 10 progesterone\$.tw. (74873)
- 11 (medroxyprogesterone acetate or MPA).tw. (25898)
- 12 dydrogesterone.tw. (413)
- 13 (norethisterone or norethindrone).tw. (3167)
- 14 HRT.tw. (9055)
- 15 (hormone adj1 therap\$).tw. (11962)
- 16 (estrogen\$ or oestrogen\$).tw. (142386)
- 17 estradiol\$.tw. (73298)
- 18 CEE.tw. (1055)
- 19 conjugated equine estrogen\$.tw. (1157)
- 20 premarin.tw. (506)
- 21 estriol.tw. (4005)
- 22 oestradiol.tw. (12633)
- 23 (mestranol or estrone).tw. (9155)
- 24 or/6-23 (346991)
- 25 5 and 24 (38329)
- 26 randomized controlled trial.pt. (429552)
- 27 controlled clinical trial.pt. (91634)
- 28 randomized.ab. (368786)
- 29 placebo.tw. (183239)
- 30 clinical trials as topic.sh. (179204)
- 31 randomly.ab. (262645)
- 32 trial.ti. (161272)

- 33 (crossover or cross-over or cross over).tw. (71021)
- 34 or/26-33 (1089025)
- 35 exp animals/ not humans.sh. (4306043)
- 36 34 not 35 (1002924)
- 37 25 and 36 (8009)

Appendix 4. Embase search strategy

Ovid platform

From inception to 5th September 2016

- 1 exp "menopause and climacterium"/ or exp menopause/ or exp postmenopause/ or exp premenopause/ (100290)
- 2 (postmenopaus\$ or post-menopaus\$ or post menopaus\$).tw. (70911)
- 3 (perimenopaus\$ or peri-menopaus\$ or peri menopaus\$).tw. (5362)
- 4 (climacter\$ or menopaus\$).tw. (60743)
- 5 or/1-4 (135983)
- 6 exp hormone substitution/ (45945)
- 7 exp estrogen therapy/ (15437)
- 8 HT.tw. (68139)
- 9 exp gestagen/ (147348)

- 10 Progestin\$.tw. (11594)
- 11 progestogen\$.tw. (5353)
- 12 progesterone\$.tw. (80542)
- 13 (medroxyprogesterone acetate or MPA).tw. (28766)
- 14 dydrogesterone.tw. (517)
- 15 (norethisterone or norethindrone).tw. (2885)
- 16 HRT.tw. (12399)
- 17 (hormone adj1 therap\$).tw. (15869)
- 18 (estrogen\$ or oestrogen\$).tw. (162017)
- 19 estradiol\$.tw. (79497)
- 20 CEE.tw. (1377)
- 21 conjugated equine estrogen\$.tw. (1319)
- 22 premarin.tw. (2850)
- 23 estriol.tw. (3812)
- 24 oestradiol.tw. (12169)
- 25 or/6-24 (452498)
- 26 5 and 25 (55119)
- 27 Clinical Trial/ (866278)
- 28 Randomized Controlled Trial/ (416151)
- 29 exp randomization/ (71920)
- 30 Single Blind Procedure/ (22979)
- 31 Double Blind Procedure/ (131292)
- 32 Crossover Procedure/ (48506)
- 33 Placebo/ (280258)
- 34 Randomi?ed controlled trial\$.tw. (142786)
- 35 Rct.tw. (21407)
- 36 random allocation.tw. (1556)
- 37 randomly allocated.tw. (25534)
- 38 allocated randomly.tw. (2152)
- 39 (allocated adj2 random).tw. (762)
- 40 Single blind\$.tw. (17901)
- 41 Double blind\$.tw. (165293)
- 42 ((treble or triple) adj blind\$).tw. (588)
- 43 placebo\$.tw. (238306)
- 44 prospective study/ (349547)

- 45 or/27-44 (1614380)
46 case study/ (39807)
47 case report.tw. (313200)
48 abstract report/ or letter/ (971946)
49 or/46-48 (1317703)
50 45 not 49 (1572737)
51 26 and 50 (14243)

Appendix 5. PsycINFO search strategy

From 1806 to 5th September 2016

Ovid platform

- 1 exp menopause/ (3311)
2 (postmenopaus\$ or post-menopaus\$ or post menopaus\$).tw. (2599)
3 (perimenopaus\$ or peri-menopaus\$ or peri menopaus\$).tw. (635)
4 (climacter\$ or menopaus\$).tw. (4484)
5 or/1-4 (6036)
6 exp hormone therapy/ (1853)
7 HT.tw. (11590)
8 exp progestational hormones/ (2155)
9 Progestin\$.tw. (576)
10 progestogen.tw. (107)
11 progesterone\$.tw. (3764)
12 (medroxyprogesterone acetate or MPA).tw. (572)
13 dydrogesterone.tw. (9)
14 (norethisterone or norethindrone).tw. (41)
15 HRT.tw. (549)
16 (hormone adj1 therap\$).tw. (922)
17 (estrogen\$ or oestrogen\$).tw. (7529)
18 estradiol\$.tw. (5322)
19 CEE.tw. (147)
20 conjugated equine estrogen\$.tw. (72)
21 premarin.tw. (38)
22 estriol.tw. (52)
23 oestradiol.tw. (440)
24 or/6-23 (25236)
25 5 and 24 (2144)
26 random*.ti,ab,hw,id. (156444)
27 trial*.ti,ab,hw,id. (145619)
28 controlled stud*.ti,ab,hw,id. (10362)
29 placebo*.ti,ab,hw,id. (34986)
30 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id. (24854)
31 (cross over or crossover or factorial* or latin square).ti,ab,hw,id. (24751)
32 (assign* or allocat* or volunteer*).ti,ab,hw,id. (135461)
33 treatment effectiveness evaluation/ (20144)
34 mental health program evaluation/ (1962)
35 exp experimental design/ (51656)
36 "2000".md. (33542)
37 or/26-36 (435984)
38 25 and 37 (615)

Appendix 6. CINAHL search strategy

From 1982 to 5th September 2016

Ebsco platform

#	Query	Results
S38	S25 AND S37	3,344
S37	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	1,071,060
S36	TX allocat* random*	5,230
S35	(MH "Quantitative Studies")	14,815
S34	(MH "Placebos")	9,793
S33	TX placebo*	39,352
S32	TX random* allocat*	5,230
S31	(MH "Random Assignment")	41,527
S30	TX randomi* control* trial*	109,343
S29	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	848,664
S28	TX clinic* n1 trial*	189,022
S27	PT Clinical trial	79,712
S26	(MH "Clinical Trials+")	202,243
S25	S6 AND S24	9,967
S24	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	58,243
S23	TX mestranol or estrone	242
S22	TX oestriol	15
S21	TX estriol	326
S20	TX premarin	53
S19	TX conjugated equine estrogen*	246
S18	TX CEE	812
S17	TX estradiol	4,345
S16	TX estrogen* or TX oestrogen*	14,167
S15	TX hormone N1 therap*	19,141
S14	TX norethisterone or TX norethindrone	182

(Continued)

S13	TX hydrogesterone	39
S12	TX medroxyprogesterone acetate or TX MPA	16,317
S11	TX progesterone	4,342
S10	TX progestogen	459
S9	(MM "Progestational Hormones+") OR (MM "Medroxyprogesterone Acetate") OR (MM "Estrogens+")	6,252
S8	TX HT or TX HRT	10,069
S7	(MM "Hormone Replacement Therapy+") OR (MM "Hormone Therapy+")	5,753
S6	S1 OR S2 OR S3 OR S4 OR S5	25,078
S5	TX hot flush* or TX hot flash*	2,572
S4	TX climacter* or TX menopaus*	14,243
S3	TX perimenopaus* or TX peri-menopaus* or TX peri menopaus*	3,419
S2	TX postmenopaus* or TX post-menopaus* or TX post menopaus*	13,673
S1	(MM "Climacteric+") OR (MM "Perimenopause") OR (MM "Perimenopausal Symptoms+") OR (MM "Menopause+") OR (MM "Hot Flashes")	10,339

Appendix 7. Trials registers search strategy

www.clinicaltrials.gov:

hormone and menopausal and random

The World Health Organisation International Trials Registry Platform search portal:

hormone + menopausal

Appendix 8. Data extraction domains

Data were extracted from the primary studies on the following study characteristics:

Trial characteristics

1. Method of randomisation
2. Method of allocation concealment
3. Use of stratification
4. Adequacy of double-blinding (i.e. an explicit statement that therapies could not be distinguished by appearance or administration route, or both)
5. Number of participants screened for eligibility, randomised, analysed, excluded, lost to follow-up or dropped out (i.e. withdrew from the study but were followed up)
6. Level of adherence to therapy
7. Whether an intention-to-treat analysis was done
8. The use of a power calculation to estimate sample size
9. Duration, timing and location of the study
10. Study design (e.g. parallel or cross-over, single-centre or multi-centre)
11. Source of funding

Characteristics of study participants

1. Inclusion and exclusion criteria
2. Age and any other recorded characteristics of women in the study
3. Menopausal status (i.e. peri- or postmenopausal and how status was defined, surgical or natural menopause) of the women in the study
4. Baseline equality of treatment groups
5. Means of recruitment

WHAT'S NEW

Date	Event	Description
6 January 2017	New citation required and conclusions have changed	<p>The addition of 2 new studies and changes in review outcomes have led to changes in the conclusions of this review.</p>
6 January 2017	New search has been performed	<p>New included studies:</p> <ul style="list-style-type: none"> • KEEPs 2012 • ELITE 2014 <p>New excluded studies:</p> <ul style="list-style-type: none"> • AHT 2015; Paoletti 2015; Rasgon 2014; Schierbeck 2012; SMART 2016 (new exclusions) • Haines 2003; Nielsen 2006 (previously included, as quality of life is no longer a review outcome) • Pefanco 2007 (previously included, now excluded, as specific (not global) measures of cognition are no longer a review outcome) <p>WHI changes:</p> <ol style="list-style-type: none"> 1. Updated WHI 1998 to include data from follow-up publications 2. Mean intervention period of combined WHI 1998 corrected from 5.2 years to 5.6 years (corresponding with the date when women were instructed to stop taking the medication) (see Chlebowski 2003)

HISTORY

Protocol first published: Issue 2, 2003
 Review first published: Issue 3, 2005

Date	Event	Description
31 October 2012	Amended	<p>Correction to 'Characteristics of included studies' table and description of studies, related to sample numbers for ESPRIT 2002 and HERS 1998</p> <p>No change to data or analyses</p>
3 February 2012	New citation required and conclusions have changed	<p>Search updated to February 2012</p> <p>New studies: Greenspan 2005; Nielsen 2006; Pefanco 2007; Tierney 2009</p> <p>Updated WHI 1998 for the following outcomes: lung cancer (Chlebowski 2009, Chlebowski 2010a), breast cancer (Chlebowski</p>

Date	Event	Description
		2010), cognition in older women (Espeland 2010; Resnick 2009), colorectal cancer (Prentice 2009a; Ritenbaugh 2008), clinical outcomes at 7.1 and 10.7 yrs in oestrogen-only HT arm (LaCroix 2011) and at 7.9 years in combined arm (Heiss 2008)
		Updated EPHT for quality of life (Veerus 2008)
		Updated WISDOM for quality of life (Welton 2008)
		Reclassified equivalent HT doses in line with Australian Menopause Society recommendations: amended table of comparisons for studies using oral oestradiol (n = 10)
		Added 'Summary of findings' table and absolute risks, updated Discussion and Conclusions sections
11 February 2009	New citation required but conclusions have not changed	Review updated June 2008
31 May 2008	New search has been performed	<p>Added the following new studies:</p> <p>Barakat 2006, EPHT 2006, WISDOM 2007, Yaffe 2006.</p> <p><u>WHI 1998 oestrogen-only arm, data added:</u></p> <p>Venous thromboembolism at 2 & 7.1 years' follow-up</p> <p>Coronary heart disease, venous thromboembolism, stroke, breast cancer, fracture and quality of life at 7.1 years' follow-up</p> <p><u>WHI 1998 combined arm, data added:</u></p> <p>Subgroup analysis of breast cancer risk by prior hormone summarised in the text (Discussion section)</p> <p>Data on main outcomes after 3 years post intervention (Discussion section)</p> <p>Results from WHI 1998 (WHISCA) on specific cognitive functions in older women added to the text</p> <p>No substantial changes to overall findings of this review. Statistically significant risk of venous thromboembolism for WHI oestrogen-only arm now evident at follow-up "up to 2 years"</p>
18 May 2008	Amended	Converted to new review format
20 November 2003	New citation required and conclusions have changed	Substantive amendments made

CONTRIBUTIONS OF AUTHORS

For the 2017 update of the review, Jane Marjoribanks (JM) extracted and entered data and drafted the text, and Jasmine Lee (JL) checked study selection and data extraction. Helen Roberts (HR), Cindy Farquhar (CF) and Anne Lethaby (AL) commented on and contributed to the drafts.

For the 2008 and 2012 updates of the review, JM extracted and entered data and drafted the text, and CF checked study selection and data extraction. HR, CF and AL commented on and contributed to the drafts.

CF and AL developed the original protocol and circulated it to members of the Cochrane HT Study Group for comment. The following people contributed specifically to the protocol: Professor Shah Ebrahim, Dr Peter Tugwell, Teresa Moore and Maria Judd. For the original version of the review, JM and Jane Suckling searched for relevant studies and selected studies for inclusion, and JM extracted and entered data that were checked by Quirine Lamberts. JM drafted the review, circulated it to other members of the Cochrane HRT Study Group for comment and edited the draft.

The following individuals commented on the draft of the original review: Breast Cancer Group: Sue Carrick, Sue Lockwood (Editor); Dementia and Cognitive Improvement Group: Professor Leon Flicker (Editor), Professor Lon Schneider (Editor); Heart Group: Lee Hooper (Editor), Theresa Moore (Review Group Coordinator); Gynaecology and Fertility Group: Cindy Farquhar (Co-ordinating Editor), Anne Lethaby (Editor); Stroke Group: Professor Ale Agra (Editor), Steff Lewis (Statistical Editor).

DECLARATIONS OF INTEREST

Cindy Farquhar is a director/shareholder of a gynaecology clinic and undertakes private practice within those premises. She has received travel/accommodation/meeting expenses from ESHRE or ASRM for attendance at scientific meetings.

JL, AL, JM and HR have no interests to declare.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, New Zealand.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2017 update, we decided to omit quality of life as an outcome and to focus on adverse events only, to make the review more concise. This meant that we excluded two previously included studies ([Haines 2003](#); [Nielsen 2006](#)).

We also decided for the 2017 update to limit the outcome "Cognitive function" to studies of global measures of cognition, also to keep the review as concise as possible. This did not change any of our data.

For the 2017 update, we did not include studies that did not report any events in either group for a particular outcome in the meta-analysis for that outcome because they did not add useful data ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Perimenopause; *Postmenopause; Cardiovascular Diseases [chemically induced] [mortality]; Cause of Death; Estrogen Replacement Therapy [*adverse effects] [methods]; Estrogens [*adverse effects] [therapeutic use]; Hot Flashes [drug therapy]; Neoplasms [chemically induced] [mortality]; Progesterone [*adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Venous Thromboembolism [chemically induced]

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Middle Aged